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Liquisolid systems as a novel approach in formulation and manufacturing of solid dosage forms: Challenges and perspectives

Ivana Aleksić*, Teodora Glišić, Jelena Parojčić

University of Belgrade – Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, Vojvode Stepe 450, 11221 Belgrade, Serbia

*Corresponding author: Ivana Aleksić, E-mail: ivana.aleksic@pharmacy.bg.ac.rs

Abstract

Liquisolid systems are a novel, promising platform for the production of solid dosage forms with a high liquid content, i.e. dispersion of the drug in a suitable, hydrophilic, non-volatile liquid vehicle or liquid drug. This technology requires conventional, but highly porous excipients (carrier and coating material in the appropriate ratio) able to absorb/adsorb liquid medication, resulting in both good flowability and acceptable compression properties. This approach has shown great potential to improve the dissolution rate and bioavailability of poorly soluble drugs, and has been recognized as a good alternative to common, more complex and expensive techniques. A variety of applications of this simple technique have been investigated recently, including the preparation of: modified release tablets, orally disintegrating tablets, solid dosage forms with liquid herbal extracts, etc. This emerging technology has numerous advantages, and the most important are: simplicity, cost-effectiveness, applicability in large scale production and environmental friendliness. However, it is accompanied by certain challenges as well, such as limited applicability in the case of highly dosed drugs. This article aims to give a comprehensive overview of recent progress regarding the potential applications of this technology, as well as to give an insight into the new liquisolid-based techniques intending to further support its commercial applicability.

Key words: porous excipients, tablets, multiparticulate systems, poorly soluble drugs, improved bioavailability

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Introduction

Apart from the considerable number of poorly water-soluble active pharmaceutical ingredients (APIs) that are already on the market, an increasing number of drug candidates with highly lipophilic structure and low aqueous solubility has directed research efforts in the last two decades towards development of various formulation approaches for improving bioavailability of orally administered drugs (1). Numerous approaches have been developed and have shown the potential to improve solubility and dissolution rate, including different methods for API particle size reduction (e.g. API micronization), improvement of API solubilization in gastrointestinal fluids (e.g. lipid-based formulations in soft gelatin capsules), modification of API solid state (e.g. amorphous solid dispersions) (2). Most of the investigated methods, although promising in laboratory settings, show highly challenging clinical translation potential. Namely, production processes are often complex and cost-demanding, require special equipment and/or specific analytical methods for quality control, which altogether makes the scale-up difficult and often leads to low batch-to batch reproducibility (3). Furthermore, some of the formulation strategies for poorly water-soluble APIs involve the use of organic solvents and/or energy intensive processes which considerably contribute to the carbon footprint and raise environmental concerns. Formulation of (amorphous) solid dispersions is, for example, one of the most commonly applied methods, and despite decades of intensive research in this area, there is still a limited number of marketed products based on this technology. The underlying reasons are related to physical stability issues, as well as to manufacturing processes that are usually classified into solvent-based (e.g. spray drying) and melting methods (e.g. hot melt extrusion). It is important to note that physical instability issues, such as conversion of the API from amorphous to a crystalline form, can be provoked by numerous factors, including those related to thermal or mechanical stress during manufacturing process. Although a variety of manufacturing techniques have been developed, the major challenges for a wider industrial production of solid dispersions are the still complex scale-up, high processing temperatures, high energy consumption, usage of organic solvents and low process reproducibility (4).

Liquisolid technology as a promising, yet simple and cost-effective approach for the bioavailability enhancement, stood out from the commonly applied more complex techniques and gained increased research attention during the last decade. The application of this approach not only to improve dissolution rate of poorly soluble APIs, but also to prepare modified release preparations, solid dosage forms with liquid APIs or liquid herbal extracts, has also been investigated. This paper aims to review the potentials for various applications of liquisolid systems and the challenges for their manufacturing in industrial settings, as well as novel solutions to overcome the limitations. A comprehensive review of different applications of liquisolid systems that include novel, liquisolid-based technologies has not been reported in the literature so far.

Liquisolid system formulation approach

The formulation of soft gelatin capsules containing a liquid dispersion of a poorly soluble API represents one of the most frequently applied methods to enhance the API dissolution rate and consequently bioavailability. Soft gelatin capsules also represent a practically unique approach for preparation of solid dosage forms with oily liquid APIs. The production of soft gelatin capsules is rather costly and requires specific production equipment, which initiated the development of a new concept in the 1990s, the so-called "powdered solution technology" (5). This technique considered simple mixing of a solution of a poorly soluble API in a non-volatile hydrophilic solvent, or a liquid API with powder able to adsorb liquid (e.g. cellulose and silica) and form dry and acceptably flowable powder. Powdered solutions enabled a rapid release of the poorly soluble API, due to the fact that the API is already in solution, similar to soft gelatin capsules. Although improved dissolution properties of poorly water-soluble APIs from powdered solutions have been demonstrated, this concept lacked industrial applicability due to the limited flowability and poor compressibility, i.e. the compression of these formulations led to the liquid "squeezing out" phenomena and loss of a certain amount of the API. Therefore, as a subsequent technology, liquisolid (LS) systems involved simultaneous consideration of both flowability and compression characteristics (6).

LS systems were defined as dry-looking, non-adherent admixtures of liquid and powder that possess acceptable flowability and, simultaneously, acceptable compression characteristics. Liquid, i.e. liquid medication is a liquid lipophilic API or solution/suspension of a poorly water-soluble API in a non-volatile, water miscible solvent. The powder used for preparation of LS systems includes a carrier material that is porous and able to absorb liquid into the inner pores, as well as to adsorb the additional liquid onto the particles' surface, and a coating material that possesses highly adsorptive, fine particles able to adsorb any excess liquid from the surface of the carrier particles loaded with the liquid medication. LS compacts were defined as immediate or sustained release tablets or capsules that are prepared from LS powder and additional excipients, such as lubricant, binder, disintegrant, if needed. The corresponding patent aimed to ensure the applicability of this concept to an industrial scale, emphasizing that a certain system of carrier and coating material can retain only certain amount of liquid while maintaining acceptable flowability and compression properties at the same time (6). Therefore, a mathematical approach to the formulation of LS systems has been proposed by Spireas and Bolton (6). An important parameter is the carrier to coating ratio (R) that represents the ratio between the quantities of carrier (Q) and coating (q) materials. By applying the "liquisolid flowability test" for a certain R value, the "flowable liquid load factor" ($^{\Phi}L_f$), representing the maximum liquid load resulting in acceptable flowability, can be determined. Liquid load factor (L_f) is the ratio of the amount (in grams) of liquid (W) over the quantity of carrier (Q). While for the former "powdered solution technology" a specific method "angle of slide" and the limiting value of 33° were used for assessing flowability, for LS systems the commonly used powder flow rate can be assessed. An LS powder should exhibit consistent flow without blockages, and the

limiting value for powder flow rate should be determined depending on the requirements of the specific equipment used for further processing (tableting or capsule filling machine). Considering that it was recognized that even with LS admixture possessing good flowability, problems could occur during compaction, thus hindering its processability on the industrial scale, a relatively simple method for evaluation of LS system compactibility has been proposed and named "the liquisolid compressibility test". A detailed description of the procedure for the evaluation of compression properties of admixtures with different R values and increasing amounts of liquid phase, as well as mathematical equations used to determine powder excipient specific physical properties, are provided in corresponding patent (6). This test considers the determination of a specific parameter, "pactisity", which is the resistance to crushing of a one-gram tablet prepared by compressing the LS system under the compression pressure resulting in maximum tablet resistance to crushing. An acceptably compressible admixture has a pactisity greater than or equal to 20kg/g, while no liquid squeezed out during compression should be observed. "Compressible liquid load factor" ($^{\Psi}L_f$) considers the maximum liquid load resulting in acceptable compressibility defined by the abovementioned criteria. For a given R value, finally, the optimum load factor (L_o) should be determined considering both flowability and compactability, i.e., by using the following equations (6, 7):

$L_o = {}^{\Phi}L_f$ when ${}^{\Phi}L_f < {}^{\Psi}L_f$

$L_o = {}^{\Psi}L_f$ when ${}^{\Phi}L_f > {}^{\Psi}L_f$

The proposed mathematical equations allow the calculation of the excipient specific formulation parameters that could further facilitate the calculation of the optimum quantities for a certain system. These equations, as well as the criteria for the acceptably compressible admixture, were based on the properties of common excipients, such as microcrystalline cellulose and silica, and should be reconsidered in the case of novel excipients with considerably higher specific surface area and adsorption capacity (8). However, the idea behind the proposed formulation approach, i.e., the importance of considering both flowability and compaction properties of the admixtures at the same time, is of utmost importance for a wider applicability of the LS technology.

Components of liquisolid formulations

The preparation of an LS system involves a simple mixing procedure, schematically represented in Figure 1. Spireas (7) described in detail the preparation procedure in a mortar with the aid of a pestle, and in a few studies it has been shown that the equipment commonly used for solid dosage forms production, such as a fluid bed processor (9, 10) or an extruder/spheronizer, could be used for the production of LS systems (11, 12). The excipients required for the preparation of an LS system involve: a carrier, coating material and liquid vehicle (if liquid medication represents the dispersion of an API in a suitable liquid).

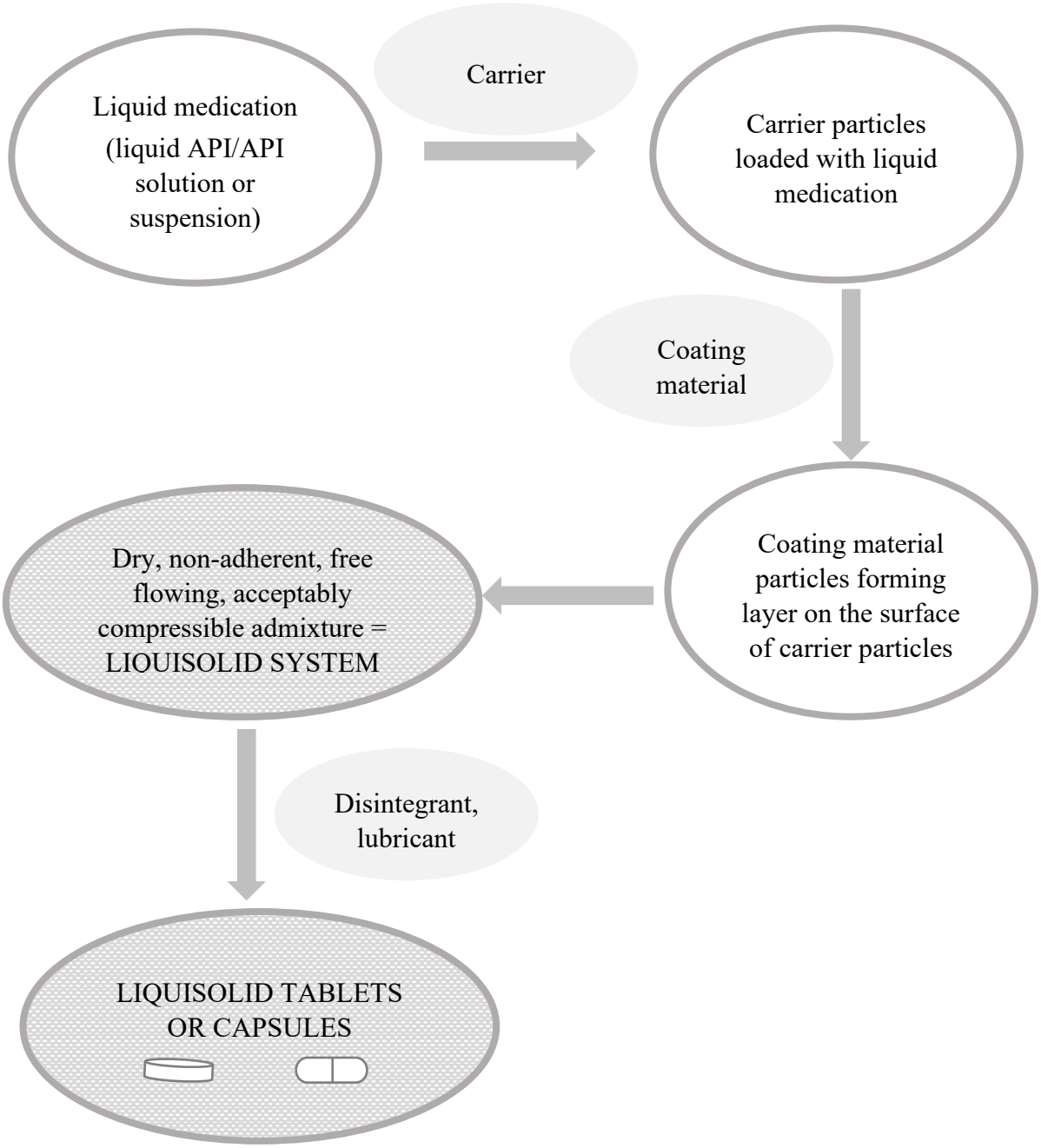

Figure 1. Schematic representation of liquisolid system preparation
Slika 1. Šematski prikaz pripreme tečno-čvrstih sistema

The carrier should be an excipient with a porous nature and high specific surface area that is able to absorb a considerable amount of liquid. The most commonly used carrier is certainly microcrystalline cellulose (MCC), but other conventional excipients, such as amorphous cellulose (7), starch, lactose, sorbitol (13) were used. Novel highly porous excipients with a significantly higher absorption capacity, e.g. Fujicalin®

(anhydrous dibasic calcium phosphate), Neusilin® US2 (amorphous form of magnesium aluminometasilicate) (9, 14), Syloid® XDP 3050 and Syloid® XDP 3150 (mesoporous, amorphous silica) (15) were also investigated as potential carriers in LS systems. In order to achieve sustained drug release, hydrophobic carriers such as quaternary polymethacrylates Eudragit® RL and RS were also used as carriers in LS compacts (16).

Upon saturation of the carrier's inner pores with liquid phase, adsorption of the liquid and formation of the liquid layer on the surface of the carrier particles will occur. Particles of the coating material have a role in adsorbing the excess liquid present on the surface of the carrier particles, thus ensuring that the powder is dry-looking and free flowing. The coating material should therefore have a high adsorption capacity and very fine particles (preferably 10 to 5000 nm in diameter). The most frequently used coating material is colloidal silica (Aerosil® 200). Other excipients used as coating materials include: Neusilin® UFL2 (17), Florite® (calcium silicate) (18), Syloid® 244 FP (mesoporous amorphous silica) (19) and crospovidone (11, 12).

Unlike solid self-emulsifying drug delivery systems that consider a liquid lipid-based formulation adsorbed onto the porous excipient, LS systems represent a different approach to the bioavailability enhancement of poorly water-soluble APIs, where a simple solution or suspension of the API in a suitable hydrophilic solvent is converted into a non-adherent powder by using a carrier and coating material. Liquid vehicles used for LS formulations should be: non-volatile, i.e. with a high boiling point (considering that the liquid phase remains loaded on the carrier, with no drying step involved), water-miscible, and preferably not highly viscous organic solvents, such as propylene glycol, liquid macrogols, glycerol, and polysorbates (7). Cremophor® EL (macrogolglycerol ricinoleate) was also shown to be a suitable liquid vehicle in LS systems with poorly soluble APIs (12, 20, 21). The solubility of the API should also be considered when selecting the liquid vehicle, since higher API solubility in the selected solvent can lead to lower tablet weight (due to the lower required quantities of porous excipients), as well as to a higher fraction of molecularly dispersed API, which contributes to the dissolution rate enhancement (22).

Some additional excipients may be needed for the preparation of LS compacts (tablets or capsules) (7). In the case of immediate-release preparations, the most important ones are disintegrants enabling faster wetting and disintegration of LS compact, thus ensuring that disintegration is not a rate-limiting step for the drug dissolution. Superdisintegrants, such as sodium starch glycolate, croscarmellose sodium and crospovidone, are the most commonly used in LS formulations (23). A suitable lubricant may also be included in the LS compact formulation. In the case of the sustained-release LS compacts, the addition of a suitable binder, i.e. matrix-forming agent (e.g., hydroxypropylmethyl cellulose, HPMC), is recommended (7).

Advantages and limitations of liquisolid technology

LS technology as an approach for the production of solid dosage forms with a high liquid content offers numerous advantages, including the following (7, 22):

- Improved dissolution profile and, consequently, bioavailability of poorly soluble APIs;
- Sustained release formulations with zero order release can be prepared;
- Solid dosage forms (tablets or capsules) with liquid APIs can be prepared;
- The preparation technique is simple, cost-effective and environmentally friendly;
- Common production equipment for solid dosage forms can be used;
- Conventional excipients can be used for a LS system preparation;
- It has a great potential for large-scale production.

Although highly promising, this technique is accompanied by certain challenges calling for future research efforts, and some of them involve (7, 8, 22):

- The formulation of LS systems with high dose APIs is highly challenging due to the required large quantity of liquid vehicle, and thus large carrier and coating material quantities, which may lead to unacceptable weight of unit dosage form;
- High solubility of the API in selected non-volatile solvent is preferable;
- The optimum quantities of porous excipients are liquid phase specific and have to be carefully determined;
- Despite being apparently dry and showing good flowability, LS admixture could still exhibit compression difficulties, particularly during tableting on modern industrial high-speed tablet presses;
- More thorough investigations into the compaction behavior of LS systems and factors affecting it would facilitate industrial application of the LS technology.

Regarding the challenges associated with preparation of LS compacts with APIs that require higher therapeutic doses, the addition of polyvinylpyrrolidone (PVP) in the liquid phase has been suggested as a possible way to considerably reduce the required amount of carrier and coating material. PVP can act as a binder during compaction, which may enable higher liquid loads. Another benefit ascribed to the addition of PVP in liquid phase is inhibition of the precipitation of API in supersaturated liquid medication (7, 24-26). The introduction of novel mesoporous excipients has also allowed significantly higher liquid loads, i.e. a higher amount of the API incorporated in LS system, in comparison with common carriers such as MCC. Further enhancements aiming to expand the applicability of the LS concept in the case of high-dose APIs are expected and present the subject of some recent investigations described in the section *Novel liquisolid-based techniques*.

Studies addressing the lack of knowledge regarding compaction behavior of liquisolid systems are still scarce. Apart from several studies reported in the last years that involve the analysis of mechanical properties (resistance to crushing, friability) of liquisolid tablets (18, 27-32), there are only a few recent studies dealing more thoroughly with factors influencing compaction behavior of liquisolid systems (14, 19), including recent papers of our research group (8, 9). These studies revealed that the influence of

different formulation and process parameters can significantly affect compaction behavior of LS systems and that the use of dynamic compaction analysis and mathematical models for the evaluation of compression properties could contribute to a better understanding and facilitate the optimization of the formulation and production process of LS tablets. Furthermore, the results of our recent study indicate that the application of SeDeM Expert System could be a useful tool for liquisolid system processability evaluation (11).

Applications of the liquisolid technology

Drug dissolution enhancement

Over the years, the LS technique has been extensively researched as a way to improve the dissolution and bioavailability of poorly soluble APIs. Several mechanisms of improved drug dissolution from LS systems have been proposed (25):

- Increased drug surface area available for release, due to the presence of drug molecules/particles dispersed in the liquid vehicle, with a higher fraction of molecularly dispersed drug contributing to faster drug release;
- Enhanced aqueous solubility due to the liquid vehicle acting as a co-solvent in the microenvironment at the interface between the LS powder particle and dissolution medium;
- Improved wetting properties of powder particles due to the presence of the hydrophilic liquid vehicle acting as a surface active agent or having a low surface tension.

Due to their widespread application, nonsteroidal anti-inflammatory drugs (NSAIDs), most of which belong to group II of Biopharmaceutics Classification System (BCS) and are characterized by low solubility, were some of the first candidates for model APIs in LS systems (33). Javadzadeh et al. compared the dissolution rate of piroxicam from LS compacts with that from conventional directly compressed tablets and hard gelatin capsules. LS compacts contained MCC as a carrier and colloidal silica as a coating material, while polysorbate 80 was chosen as the liquid phase following previously conducted solubility studies with several potential solvents. The results of dissolution testing indicated that the LS technique greatly improved the dissolution rate of piroxicam, with 100% of the API being released from the LS compacts in 10 minutes, while at the same time frame 60% and 50% of the API was released from tablets and capsules, respectively (34). In the following study of the same research group, the effect of the carrier type and aging on the characteristics of piroxicam LS compacts, including dissolution rate and compact hardness, was examined. The study showed that after being stored in appropriate conditions for 9 months, neither hardness nor dissolution rate of compacts changed significantly (13). Tiong and Elkordy used naproxen as a model drug, with MCC, colloidal silicon dioxide and maize starch as the carrier, coating material and disintegrant, respectively. It was shown that the application of the LS technique improved the dissolution rate in comparison to directly compressed tablets of the same composition,

excluding liquid phase (Cremophor® EL or macrogol 400). The importance of formulation variables, drug concentration and the type of liquid vehicle used, and their effect on dissolution rate were also noted. The results indicated that the solubility of drug in liquid vehicle does affect the dissolution rate, but differences in porosity, compact hardness and disintegration time need to be taken into consideration as well (35). The improvement of *in vitro* dissolution rate was also noted in studies with indomethacin (36), ketoprofen (37, 38), diclofenac sodium (39) and nimesulid (40). Furthermore, a number of different APIs with low solubility were formulated as LS systems, including: methyclothiazide (41), carbamazepine (24, 42), famotidine (43), griseofulvin (44), flunarizine (45), rosuvastatin calcium (10), itraconazole (46), etc. A study with ketoconazole, another model substance with dissolution-rate limited bioavailability, showed an almost 3 times higher percentage of the API released from LS compacts compared to directly compressed tablets, prepared with the same excipients. Ketoconazole was molecularly dispersed inside the LS system, and the lack of changes in the crystalline state, as well as the absence of any interactions between API and excipients, was confirmed by solid state characterization (26).

In recent years, improved bioavailability of poorly soluble drugs formulated as LS systems was reported in a number of *in vivo* studies (47-53), including the studies performed in healthy human volunteers (27, 54). Jhaveri et al. (50), for example, conducted a study with carvedilol as a model drug. Macrogol 400 was chosen as the liquid phase, Neusilin® US2 was used as a carrier, whereas colloidal silicon dioxide was used as a coating material. The final blend contained a lubricant (magnesium stearate) and disintegrant (croscarmellose sodium) as well. Pharmacokinetic studies were carried out on Wistar rats and oral bioavailability was determined by estimating plasma concentration of the drug in selected time points. A suspension of pure carvedilol was used as a control. The results showed a statistically significant improvement of bioavailability from LS compacts, with increased absorption rate and higher plasma concentration in each of the chosen time points. These findings were in accordance with the previously obtained *in vitro* dissolution results, which showed that for all the tested LS formulations, more than 85% of drug was released in 30 minutes. In another interesting investigation involving *in vivo* studies, LS compacts were prepared in order to improve the dissolution and, consequently, antidiabetic effect of pioglitazone. LS admixtures were prepared with MCC, colloidal silicon dioxide and macrogol 400, while magnesium stearate and croscarmellose sodium were added afterwards. Both *in vitro* dissolution studies and in *vivo* studies in mice were conducted using a selected LS formulation, and the obtained results were compared to those from a directly compressed tablet of the same composition (without liquid phase) and pure drug. There was a statistically significant improvement in the drug release rate, with more than 99% of drug being released from the LS compact in 60 minutes, while only 29% was released from the directly compressed tablet and 25% from compacts containing pure drug. The reduction of blood glucose levels in tested mice when LS compacts were administered

was statistically significant, which was not achieved by either of the control treatments (32).

Development of liquisolid orally disintegrating tablets

Orally disintegrating tablets (ODTs) have numerous advantages over conventional uncoated tablets, including faster onset of action and easy application, i.e. facilitated swallowing and administration without water, which makes them particularly suitable for pediatric, geriatric, patients with swallowing difficulties, psychiatric, paralyzed, or bedridden patients (55). Formulating LS systems with various poorly soluble APIs as ODTs has attracted increasing research attention over the last years. Basalious et al. (54) aimed to formulate felodipine LS ODT that could be applied in the therapy of hypertensive crisis, an acute condition where the onset of drug action is of outmost importance. Optimized LS formulations contained 5mg of felodipine (dissolved in macrogol 400), carrier (MCC PH 102 or silicified MCC), colloidal silicon dioxide as a coating agent, crospovidone as a superdisintegrant, and suitable excipients for taste correction. Optimized LS ODTs exhibited fast disintegration both *in vitro* and *in vivo*, with disintegration times ranging between 7 and 11 seconds. A significantly higher *in vitro* dissolution rate was achieved in the case of LS ODTs, particularly those prepared with silicified MCC (Prosolv® SMCC 90) as a carrier (80% of API released in 10 minutes) in comparison with both soft gelatin capsules and conventional tablets (60% and 30% API released in 10 minutes, respectively). *In vivo* studies in healthy human volunteers showed a significantly faster felodipine absorption rate from buccally administered LS ODT containing Prosolv® SMCC 90 compared to orally administered soft gelatin capsules, indicating the suitability of LS ODTs in emergency situations. In one of the reported studies dealing with the development of LS ODT formulation, zolmitriptan was used as a model API. Zolmitriptan is used in the treatment of migraine, another condition in which rapid onset of action is very important, which together with its low bioavailability makes it a suitable model substance for the formulation of these systems. One of the objectives was to evaluate the effect of superdisintegrant type on disintegration and wetting time. LS ODTs with crospovidone showed the shortest wetting and disintegration time, and the selected LS formulation showed a significantly shorter disintegration time and faster dissolution rate compared to conventional ODTs (56). Moqbel and co-workers (57) compared two different approaches for preparation of ODTs with chlorzoxazone as a poorly soluble API that undergoes extensive first pass metabolism, and thus requires an improvement in the dissolution rate to enhance the bioavailability. Namely, ODTs were prepared by the conventional method, i.e. co-processed excipients were used for the preparation of ODTs by the direct compression process, and by the LS technology with macrogol 400 used as a non-volatile solvent. It was found that the formulation factors (e.g. carrier to coating ratio, liquid load factor) could influence wetting, disintegration time and dissolution rate of LS ODTs and should be carefully optimized. LS ODTs showed a faster wetting and disintegration time, higher dissolution rate in comparison with ODTs prepared with co-processed excipients, while

the *in vivo* studies in healthy human volunteers revealed that LS ODTs are less palatable due to the gritty feel in mouth and higher tablet weight.

Development of modified release preparations

Spireas and Bolton (41) proposed the liquisolid technology not only as an approach to enhance the bioavailability of immediate release preparations, but also as a tool to achieve sustained drug release. It has been even suggested that liquisolid systems can provide zero-order release kinetics similar to much more complex and more expensive commercial osmotic pump tablets. This relatively simple and low-cost approach involves the addition of a binder/matrix forming agent such as HPMC to a common LS formulation. Javadzadeh et al. (16) proposed a somewhat different approach to the formulation of liquisolid systems with sustained release, where Eudragit® RL or RS were used as hydrophobic carriers. Polysorbate 80 was selected as a solvent in which model highly water-soluble API (propranolol hydrochloride) showed the lowest solubility. LS compacts were prepared by the direct compression of the prepared admixture and by wet granulation with HPMC as a binder. Both LS techniques applied showed a greater retardation potential compared to conventional matrix tablets (obtained by the direct compression of the API, silica and Eudragit®), but the addition of HPMC was found to amplify the retardation effect. It was noted that besides the hydrophobic carrier, liquid vehicle can play an important role in achieving prolonged drug release. Contrary to immediate-release formulations, in the case of prolonged release preparations liquid vehicle in which the API shows lower solubility was recommended. Furthermore, it was stated that polysorbate 80 enabled the creation of a fine matrix structure, by acting as a plasticizer, i.e. contributing to the flexibility of the carrier chains and therefore keeping the API entrapped more tightly within the polymer network. Nokhodchi et al. (58) applied a similar approach in the case of theophylline as a model API, and revealed that in the case of poorly water-soluble APIs the addition of HPMC to LS formulation with hydrophobic carriers might be needed to achieve prolonged release, considering that presence of a co-solvent increases the dissolution rate of the API. In another study with a model API that has high water solubility (venlafaxine hydrochloride), it was shown that, irrespective of the carrier type, hydrophilic MCC or hydrophobic Eudragit® RS PO, polysorbate 80 as the non-volatile solvent in which API has the lowest solubility led to a slower drug release in comparison with macrogol 400 or propylene glycol. It was also observed that in the case of both carriers an increase in the R value (in the range of 2 to 8), corresponding to the higher carrier and lower coating material content, led to a slower drug release. The authors explained this by a slower diffusion of the liquid medication through a higher amount of the porous carrier material (59). However, it should be emphasized that sustained-release LS formulations are usually prepared with a considerably higher content of the coating material, i.e. lower R values (<10) in comparison with immediate-release LS systems, due to the lower absorption capacity of Eudragit® carriers (16, 58, 59). This supports the conclusion proposed by Nokhodchi et al. that a higher amount of a highly hydrophobic coating material, which is most often

colloidal silicon dioxide, also contributes to slower drug release from these formulations (25, 21). Elkordy et al. (21) also selected a non-volatile solvent in which the model API (griseofulvin) showed the lowest solubility, but, interestingly, the selected liquid vehicle solely enabled prolonged drug release from a common LS formulation containing MCC as carrier and colloidal silicon dioxide as coating material. Namely, the selected liquid vehicle was Kollicoat® SR 30 D (polyvinyl acetate aqueous dispersion stabilized with povidone and sodium lauryl sulfate), and it was postulated that this water insoluble polymer coated drug particles, thus reducing wettability and decreasing the dissolution rate. One recent study reported the application of LS technology for the development of a bilayered core-in-cup buccoadhesive tablet intended for the treatment of hypertension. The first layer presented an immediate release LS compact with olmesartan, and the second layer was a prolonged release LS compact with azelnidipine. The aim was to improve the low bioavailability of azelnidipine, bypass the first-pass effect and prolong its release and therefore its therapeutic effect. Olmesartan LS compact was prepared with Myglyol® 812 (medium-chain triglyceride) as the liquid phase, MCC as the carrier and colloidal silicon dioxide as the coating material. The final tableting blend additionally contained a filler (mannitol), superdisintegrant (sodium starch glycolate), mucoadhesive polymer (sodium carboxymethyl cellulose or chitosan), and lubricant (magnesium stearate). The prolonged release compact was prepared with mannitol, mucoadhesive polymer and colloidal silicon dioxide, while azelnidipine was dissolved in melted poloxamer 188. Ethyl cellulose was added in the last compression step to surround the double-layered tablet from three sides in order to obtain the core-in-cup system. *In vitro* release studies showed that, by applying this approach, similar olmesartan release profile can be achieved as in the case of commercial reference immediate release tablets, while it led to an improved *in vitro* release of azelnidipine in comparison with a physical mixture. The results also indicated that dissolution profiles were not affected by the bilayered form of a tablet in comparison with separate LS compacts. An *in vivo* pharmacokinetic study in healthy human volunteers was conducted with an immediate release commercially available tablet as a control. Olmesartan was rapidly absorbed and reached higher maximum plasma concentration (C_{max}) than the control, while azelnidipine showed a prolonged release profile with a significant increase in the extent of absorption (60).

Development of solid dosage forms with liquid herbal preparations

Despite the tremendously increased interest in the use of herbal medicinal products as an alternative to synthetic drugs in the last decades, studies directed towards enhancing the dosage form design and overcoming stability issues of these products are still lacking. Herbal medicinal products for oral use are available on the market predominantly as different liquid dosage forms, most commonly as tinctures or syrups. The application of liquid dosage forms is often associated with a risk of dosing errors, considering that it largely depends on the suitability of the dosing device (e.g. plastic dosing spoon, dropper, graduated syringe, dosing cup), as well as on the patient's skill and ability to properly

admeasure the required dose (61). Furthermore, issues regarding the unpleasant taste of some herbal products or stability related concerns are more prominent in the case of liquid preparations in comparison to solid dosage forms. Herbal preparations can be produced in the form of various solid dosage forms (62). Tablets and capsules are widely accepted by both patients and pharmaceutical manufacturers. However, herbal medicinal products in these dosage forms are very rarely present on the market. Soft gelatin capsules filled with liquid herbal preparations, among numerous advantages, have some disadvantages, and the most limiting one is related to the relatively complex and costly manufacturing process. On the other hand, hard gelatin capsules and tablets are usually prepared from dry herbal extracts obtained by the spray or freeze-drying process. Both of the drying procedures are energy-consuming and require special and expensive equipment. Furthermore, the products obtained can be very hygroscopic, thus raising stability issues. LS technology could be used as a suitable alternative to overcome the limitations of these commonly applied methods. However, only a few papers published recently have dealt with the application of this technique for the preparation of solid dosage forms with liquid herbal extracts (63-68). In a study comparing the influence of the preparation method, liquisolid or freeze-drying technique, the characteristics of the powders with oregano herb extract were evaluated. Liquid extracts were obtained by using combinations of a non-volatile solvent (glycerol, macrogol 400 or propylene glycol) and ethanol. LS systems were formulated with Neusilin® US2 used both as a carrier and coating material. Considering that the extraction solvent contained ethanol, drying phase as a modification to liquisolid technique was applied in order to evaporate this volatile solvent. Compared to the commonly used freeze-drying method, the application of LS technique was found to be simpler and more cost-effective. The results of dissolution testing showed that 2-3 times more rosmarinic acid and 3 times more carvacrol, as active compounds of the extract, was released from LS capsules compared to the capsules containing a freeze-dried extract. The non-volatile solvents used for extraction should also be taken into account, as it has been observed that they have a significant effect on the dissolution rate of one of the active ingredients (rosmarinic acid). LS systems have shown better flowability in comparison with the freeze-dried extract as well. Unlike freeze-dried extracts that were hygroscopic, LS capsules were stable during the whole stability testing period, and no significant differences in the release rate of rosmarinic acid and carvacrol were noticed (63). LS technology was also used to prepare tablets with oleoresin-like crude extract of *Curcuma comosa*. MCC was used as a carrier, colloidal silicon dioxide as a coating material, while the influence of the addition of propylene glycol (as non-volatile solvent) with PVP was analyzed. Croscarmellose sodium and magnesium stearate were added to tableting mixtures as well. Considering the high viscosity of this crude extract, its solution in absolute ethanol was first prepared to achieve homogenous distribution within the carrier and coating material, and afterwards ethanol was evaporated. The LS systems prepared were found to have a good flowability and compression resulted in tablets with acceptable mechanical properties. The authors observed a decrease in the resistance to crushing and disintegration time, and enhanced

dissolution with a decrease of the R value. Enhanced dissolution at lower R values has been attributed to faster disintegration and a higher amount of colloidal silica, i.e. its larger surface area exposing extract to dissolution media. The dissolution profiles of the major active compounds of the extract have been considerably enhanced by its formulation into the LS system in comparison with that from the crude extract. The addition of a non-volatile solvent resulted in increased disintegration time and slower dissolution, and it was postulated that in the case of LS systems with *Curcuma comosa* extract improved dissolution can be attributed only to the increased surface area of the extract available to the dissolution medium (64). The LS technique was used to develop colorectal-targeted delivery tablets containing natural purple rice bran oil that is used as a supplement in colorectal carcinoma treatment. The oil was converted into a dry powder using MCC and colloidal silicon dioxide, and before compression into tablets the modification of LS technique was introduced, which involved wet granulation with PVP solution in isopropanol. The obtained granules with the addition of a lubricant and disintegrant were compressed into tablets, which were then coated with Eudragit®L100 and Eudragit® NE30D in order to achieve targeted colon release. *In vitro* dissolution studies demonstrated the potential of the LS technology in converting liquid active principles/oils into solid dosage forms that can be further developed for targeted delivery (65). Silymarin is a herbal antioxidant with poor solubility and extensive first pass metabolism resulting in low bioavailability, and thus could be a suitable candidate for the formulation of a LS system. In a recent study, silymarin was dissolved in propylene glycol and a viscosity increasing agent (PVP K30 or HPMC) was added in order to increase the drug loading capacity. MCC and colloidal silicon dioxide were used as a carrier and coating material, respectively, while the prepared LS admixtures were filled into hard gelatin capsules. Compared to the capsules with the pure silymarin, both the rate and extent of release from LS capsules were greatly improved. The type of viscosity increasing agent used affected the dissolution as well as its concentration, with the best results (in terms of the rate and extent of drug released) obtained in the case of formulations containing PVP in a higher tested concentration (40%). An *in vivo* study in rats showed that the cardioprotective effect of silymarin from the LS formulation was more pronounced than the effect of pure silymarin (66). Recently reported studies introduced the modified LS technology as an approach for the preparation of tablets with liquid extracts of different *Rosaceae* family plants. Namely, this approach involved a drying step, but after the compression of a tableting mixture containing LS admixture and other suitable excipients (filler, disintegrant, and lubricant), in order to evaporate solvents used for extraction (water or ethanol). For preparation of LS admixtures, Neusilin® US2 and colloidal silicon dioxide were used as a carrier and coating material, respectively, while non-volatile solvents were not used. The authors concluded that this method can result in tablets with good mechanical properties, while fast disintegration and dissolution can contribute to better bioavailability. Furthermore, they claimed that this approach can increase the extracts' stability and the content of antioxidants in the tablet, thus

contributing to increased efficiency, while the production of an intermediate dry extract is skipped (67, 68).

Towards the lower influence of the pH value variations on drug dissolution rate

Most of the APIs are weak bases or weak acids, and therefore have pH-dependent solubility, i.e. the dissolution of these APIs is affected by the changes in the pH value of gastrointestinal fluids. El-Hammadi et al. (69) investigated the potential application of LS systems as a way to reduce the influence that the pH value and its changes along the gastrointestinal tract have on the drug dissolution rate. Loratadine was used as a model poorly-water soluble API with pH-dependent solubility. LS tablets were prepared with propylene glycol as a liquid vehicle, MCC and colloidal silicon dioxide as a carrier and coating material respectively, while sodium starch glycolate was added as a disintegrant. Dissolution studies were performed in media with different pH values (1.2, 2.5, and 5), aiming to investigate the influence of possible variations of pH values of gastric fluid. The results indicate that the application of LS systems could enhance loratadine dissolution in stomach regardless of the fed or fasted state, considering that LS tablets showed a considerably higher release rate of this weak base in comparison with both directly compressed conventional tablets and commercial tablets, particularly at higher investigated pH values. In a study with telmisartan, as a model API showing pH-dependent solubility, the application of the liquisolid technique also resulted in significantly improved dissolution and pH independent release (70). The enhanced dissolution performance of these liquisolid formulations was attributed to the improved wetting and increased surface area of the API exposed to the dissolution medium, considering that it is molecularly dispersed within the water miscible solvent (70). Badawy et al. (27) applied the liquisolid technology in order to improve the dissolution of mosapride citrate from tablets and to reduce the influence of pH variations on its dissolution rate. Dissolution studies performed by using biorelevant dissolution media revealed an enhancement in both the rate and extent of the API dissolved, as well as a reduced influence of the dissolution media pH value. The improved solubility and dissolution of the API, as proposed by the authors, can be explained by the presence of a hydrophilic solvent that diffuses into the dissolution medium along the API molecules and acts as a co-solvent in that microenvironment. It was concluded that increased thermodynamic activity of the API led to a nearly pH-independent dissolution. Furthermore, an *in vivo* pharmacokinetic study in healthy human volunteers revealed improved bioavailability of mosapride citrate from LS compacts compared to commercial tablets.

Improvement of drug photostability in solid dosage forms

Silicon dioxide is one of the most commonly used coating agents in LS systems and a substance with a high refractive index, which is why the LS technique was considered as an alternative to film coating in order to improve the photostability of active substances subject to degradation. In a study evaluating the potential of the LS technology to improve drug photostability, amlodipine was chosen as a model substance due to its

photosensitivity and formulations were prepared with MCC as a carrier, with the addition of nanometer-sized silicon dioxide and titanium dioxide as coating agents, either alone or in combinations. In order to test the photoprotective effect, the admixtures were irradiated with a light for a certain period of time, after which the content of amlodipine was determined and the results compared with the content determined in conventional film tablets after undergoing the same procedure. The content of API in the LS admixtures was ~ 97%, which was almost 20% more compared to conventional film tablets, indicating that the LS technique could be a suitable alternative to film coating for improving photostability (71).

Novel liquisolid-based techniques

Aiming to address the main challenges related to a wider industrial application of the LS technique, i.e. to enable higher liquid loads while ensuring enhanced flow and compression properties, different modifications of the LS technology have been proposed lately. One of the approaches involves a combination of the liquisolid technology and wet granulation. In a study suggesting wet granulation of LS powder prior to tableting, granulation was performed with 10% PVP solution in water, and the obtained granules showed improved flow properties. Unlike the ungranulated admixture, the obtained granules could be compressed into tablets of acceptable mechanical characteristics, and it was observed that the granulation process positively affected the *in vitro* dissolution rate of glibenclamide from tablets (72). Suliman et al. (31) proposed a similar approach, with the main difference being that in this method water as a liquid binding agent was added to the dispersion of the drug in a liquid vehicle, and the rest of the excipients were added afterwards (the so-called "water granulated LS formulations"). The observed decrease in the angle of slide values indicated improved flowability of water granulated LS admixtures. Regardless of the liquid phase (macrogol 200 or Synperonic ™ PE/L-61) used, pactisity of these compacts was higher than of those prepared with the conventional LS method. The *in vitro* dissolution studies showed an increase in the % of norfloxacin released when the new preparation method with wet granulation was used, although the significance of the increase depended on the type of liquid vehicle used as well.

An interesting liquisolid-based concept, the so-called "liquisolid pellets", was first proposed by Pezzini et al. (12) as a new preparation method for a multiparticulate system using a combination of the LS technique and extrusion–spheronization method. After the standard LS preparation process, a binding agent (copovidone aqueous solution) is added to the admixture and the obtained mass is extruded, spheronized, and pellets dried in a fluid bed system. Felodipine was chosen as a model drug and dispersed in a non-volatile solvent (macrogol 400 or Cremophor® EL). MCC was used as a carrier, while crosspovidone was added to the formulation as a coating and disintegrating agent. Conventional pellets were prepared following the same procedure, with the exclusion of the non-volatile solvent. It was observed that the LS pellets were smaller in size, with a larger pore diameter and volume compared to the conventional pellets. Felodipine LS pellets showed an improved dissolution rate in comparison with conventional pellets, with

the type of the non-volatile solvent and disintegrant concentration being recognized to affect the dissolution process. Another study conducted by the same research group deals with the use of the same technology in order to improve the dissolution rate of antiretroviral drug ritonavir. The previously described preparation method was applied, with MCC as both a carrier and a binder, while crosspovidon was chosen as a coating agent and disintegrant. Cremophor® EL and macrogol 400 were used as non-volatile solvents. One of the advancements of the LS pellet technology reported in the study was the ability to incorporate higher doses of API, which is one of the main limitations of conventional LS tablets. LS pellets prepared with Cremophor® EL showed both the highest rate and extent of drug release among the tested formulations, which confirmed that the type of non-volatile solvent used is one of the most important variables affecting drug release from these systems (73). In a following study of this research group, mixture experimental design was applied for LS pellets with each of these solvents in order to evaluate the influence of formulation parameters (concentrations of the solvent, carrier, coating material/disintegrant) on the critical quality attributes of LS pellets (74). In a recent study of our research group, liquisolid pellets were prepared by a combination of the liquisolid technology and extrusion (water granulation)-spheronization. LS pellets were prepared with MCC as a carrier and crosspovidone or silicon dioxide as a coating material, while the ibuprofen solution in macrogol 400 was used as liquid phase. LS pellets with a very high liquid load (up to 52%) exhibiting excellent flowability were obtained, confirming the great potential of this combined technique to improve the dissolution rate of high-dose poorly soluble APIs and yet preserve industrial feasibility (11). Carvacrol is a natural product, an active component of essential oil from the plant Thymus vulgaris, and a good candidate for LS system formulation because of its liquid nature. In a study dealing with the preparation of pellets with this active ingredient, three different methods were used to prepare carvacrol LS matrices with PVP, stearic acid or colloidal silicon dioxide. The obtained matrices were then mixed with the additional excipients and granulated with distilled water, following the application of extrusion and spheronization to prepare pellets. All of the prepared pellets showed acceptable drug release profiles. However, pellets containing PVP were found to have the most suitable properties and showed the slowest dissolution rate (75).

Another approach based on a combination of LS technology and extrusion-spheronization, which is named “liqui-mass technology”, was proposed more recently by Lam and associates as a new approach that can improve the dissolution of poorly soluble APIs while allowing high liquid loads (i.e. high dose of API) in liqui-pellets (filled into capsules) or liqui-tablets as dosage forms. Despite its similarities with the LS technique in terms of excipients used, the main difference is that the obtained liquid-mass system is not always a free flowing powder, but rather a wet mass or paste intended for further processing. Similar to the LS technology, liqui-mass system can be used to obtain pellets or tablets with immediate or sustained drug release (76). In the first paper reported by Lam et al. (76), naproxen was used as a model drug to formulate liqui-pellets with MCC and colloidal silicon dioxide as a carrier and coating material, respectively, while several

solvents were chosen as liquid vehicles. The prepared admixture was mixed with an adequate amount of deionized water in order to obtain a wet mass of optimal plasticity for extrusion and spheronization. The obtained pellets were dried in an oven at an appropriate temperature. The prepared liqui-pellets showed excellent flow properties despite a high liquid load factor (L_f=1). Enhanced drug release from liqui-pellets in comparison with pellets without liquid vehicle was observed, but was highly influenced by the type of liquid phase used. In the following studies, the influence of different formulation variables was investigated, aiming to optimize the release rate of naproxen from liqui-pellets (77-79). Lam et al. (80, 81) have recently reported preparation of liqui-tablets by compaction of liqui-pellets. They investigated the feasibility of preparing tablets from liqui-pellets with different poorly soluble APIs, i.e. naproxen and ketoprofen, while achieving acceptable mechanical properties and drug release. The addition of Neusilin® US2, together with MCC as a carrier material, was found to improve the mechanical properties of liqui-tablets, as well as the drug release rate (80). Liqui-tablets were proposed as a suitable alternative to liquisolid compacts for formulation of tablets with higher doses of poorly soluble APIs (81). This technology was also applied to achieve a sustained release of propranolol hydrochloride. A liqui-tablet with sustained release over 24 hours was obtained by incorporating a suitable polymer, in this case Eudragit® RS PO, into the liqui-mass system. It was emphasized that sustained drug release from liqui-tablets can be attributed to the synergistic retarding effect of the liquid vehicle and polymer, with the concentration of polymer recognized as the most important variable (82).

The reduction of particle size has been widely used as a method to improve the dissolution rate of poorly soluble APIs. Nazem et al. (83) aimed to combine co-grinding and the LS technique in order to improve celecoxib dissolution from tablets. API was dispersed in macrogol 200 and then milled in order to obtain a liquid medication that can be converted into a dry powder using suitable excipients. Physical mixture and conventional LS tablets (prepared using the standard preparation method without milling) were prepared as a comparison. Co-ground LS formulation had a better dissolution rate compared to both controls, releasing 7.5 times more drug than the physical mixture in the first 15 minutes. This is attributed to the reduced particle size and therefore improved wettability and solubility of the drug in a non-volatile solvent.

Modifications of LS technology in terms of the nature of liquid phase have also been investigated recently. Tong et al. (84), for example, used the combination of self-nanoemulsifying and LS techniques to formulate tablets, with the aim of improving compliance and oral bioavailability of vitamin K1 (VK1) which is an oily liquid, usually administered intramuscularly or intravenously. An optimized self-nanoemulsifying drug delivery system (SNEDDS), prepared by mixing VK1 with surfactants (soybean lecithin and glycocholic acid) and cosurfactant (Transcutol HP), was converted into a LS system using Fujicalin® as both a carrier and a coating material. The prepared powder was then compressed into LS tablets with the addition of necessary excipients. LS tablets achieved a higher dissolution rate than the tablets containing pure VK1 instead of SNEDDS, with

more than 80% of drug being released at pH 6.8 in the first 5 minutes, as opposed to 0% being released from tablets with pure VK1 under the same conditions. Pharmacokinetic profiles (*in vivo* study performed in beagle dogs) showed notably higher values of pharmacokinetic parameters (C_{max} and area under the curve, AUC) for LS compacts with a relative bioavailability of 200%. A similar approach was used in a study with eplerenone, where LS systems were prepared by loading previously developed and optimized nanoemulsions (NE) of eplerenone onto MCC as a carrier and nanometer-sized amorphous silicon dioxide as coating material. The aim was to combine the advantages of both methods, resulting in an oral solid dosage form with improved absorption of the drug, decreased liver degradation and improved bioavailability. While eplerenone NE on their own showed sustained drug release during 4h, the obtained eplerenone NE LS systems showed immediate release (90% of drug released within 45 minutes). Pharmacokinetic parameters (*in vivo* studies performed in rabbits) indicated an improvement of the rate and extent of absorption when LS systems were applied, as opposed to NE of eplerenone and conventional tablets (49).

Conclusion

LS technology has gained considerably increased research attention during the last decade, which has resulted in a variety of possible applications and advancements of this simple technique, greatly exceeding the initial idea. Being cost-effective, green technology, applicable in common solid dosage form manufacturing facilities and requiring conventional excipients, this technique is yet expected to achieve its commercial implementation, contributing to greatly enhanced bioperformance of solid dosage forms.

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Tečno-čvrsti sistemi kao novi pristup razvoju formulacija i proizvodnji čvrstih farmaceutskih oblika lekova: Izazovi i perspektive

Ivana Aleksić*, Teodora Glišić, Jelena Parojčić

Univerzitet u Beogradu – Farmaceutski fakultet, Katedra za farmaceutsku tehnologiju i kozmetologiju, Vojvode Stepe 450, 11221 Beograd, Srbija

*Autor za korespondenciju: Ivana Aleksić, E-mail: ivana.aleksic@pharmacy.bg.ac.rs

Kratak sadržaj

Tečno-čvrsti sistemi su nova, obećavajuća platforma za proizvodnju čvrstih farmaceutskih oblika sa visokim sadržajem tečnosti, odnosno disperzije lekovite supstance u pogodnom, hidrofilnom i neisparljivom tečnom vehikulumu ili same lekovite supstance u tečnom agregatnom stanju. Ova tehnologija podrazumeva upotrebu konvencionalnih, ali visoko poroznih ekscipijenasa (nosača i sredstva za oblaganje u odgovarajućem odnosu) koji mogu da absorbuju/adsorbuju tečnost uz zadržavanje dobre protočnosti i prihvatljivih svojstava pri kompresiji. Ovaj pristup je pokazao značajan potencijal da poboljša brzinu rastvaranja i bioraspoloživost slabo rastvorljivih lekovitih supstanci, a prepoznat je kao dobra alternativa uobičajeno primenjivanim, znatno složenijim i skupljim tehnikama. Pored toga, nedavno su istraživane brojne mogućnosti za primenu ove jednostavne tehnike, uključujući izradu: tableta sa modifikovanim oslobađanjem lekovite supstance, oralno disperzibilnih tableta, čvrstih farmaceutskih oblika sa tečnim biljnim ekstraktima, itd. Ova nova tehnologija pruža brojne prednosti, među kojima su najvažnije njena jednostavnost, ekonomičnost, primenljivost u industrijskoj proizvodnji i ekološka prihvatljivost. Međutim, prate je i izvesni izazovi, kao što je ograničena primenljivost u slučaju visoko doziranih lekovitih supstanci. Ovaj rad ima za cilj da pruži sveobuhvatan pregled nedavnog napretka u pogledu potencijalne primene ove tehnologije, kao i da pruži uvid u nove tehnike zasnovane na konceptu tečno-čvrstih sistema koje teže da dalje prošire njenu komercijalnu primenu.

Ključne reči: porozni ekscipijensi, tablete, višečestični sistemi, slabo rastvorljive lekovite supstance, poboljšana bioraspoloživost