Expert Opinion

Drug release from liquisolid systems: speed it up, slow it down

Ali Nokhodchi[†], Christina M Hentzschel & Claudia S Leopold
[†]*Universities of Kent and Greenwich, Medway School of Pharmacy, Chemistry and Drug Delivery Group, Chatham Maritime Kent, UK*

Introduction: Today, the properties of many new chemical entities have shifted towards higher molecular weights and this in turn increases the lipophilicity hence decreasing aqueous solubility. The low solubility of drugs usually has *in vivo* consequences such as low bioavailability, increased chance of food effect and incomplete release from the dosage form.
Areas covered: The present review discusses the advantages of the liquisolid technology in formulation design of poorly water soluble drugs for dissolution enhancement and highly water soluble drugs for slow release pattern.
Expert opinion: With the advent of high throughput screening and combinatorial chemistry, it has been shown that most of the new chemical entities have a high lipophilicity and poor aqueous solubility, hence poor bioavailability. In order to improve the bioavailability, the release rate of these drugs should be enhanced. Although there are multiple technologies to tackle this issue, they are not cost effective due to the involvement of sophisticated machinery, advanced preparation techniques and complicated technology. As the liquisolid technology uses a similar production process as the conventional tablets, this technology to improve the release rate of poorly water soluble drugs will be cost effective. This technology also has the capability to slow down drug release and allows preparing sustained release tablets with zero order drug release pattern. The excipients required for this technology are conventional and commonly available in the market. The technology is in the early stages of its development with extensive research currently focused on. It is envisaged that the liquisolid compacts could play a major role in the next generation of tablets.

Keywords: compactibility, co-solvent, dissolution enhancement, flowability, liquisolid technology, solubility, sustained release

Expert Opin. Drug Deliv. (2011) 8(2):191-205

1. Introduction

The solubility of active pharmaceutical ingredients is a matter of concern to formulators for the design of fast or slow release formulations. The development of fast release formulations for poorly water soluble drugs is not an easy task as many of new chemical entities shifted towards liphophilicity which results in decreasing water solubility [1,2]. Due to the low solubility, many of these developed formulations have bioavailability issues. It has been reported that about 40% of the drug in the development stage and 60% of synthesized drugs have poor water solubility [1,3]. One of the approaches to improve bioavailability of poorly water soluble drugs is an increase in dissolution/solubility of drugs. Although there are several techniques to enhance the dissolution rate of drugs (e.g., transformation into soluble polymorph, micronization, solid dispersion, co-grinding, preparation of salt, nanosuspension, complex formation), these techniques are not cost effective due to advanced methodologies and also sometimes

informa
healthcare

10.1517/17425247.2011.548801 © 2011 Informa UK, Ltd. ISSN 1742-5247

Article highlights.

- Liquisolid technology has been proven to be a promising technology to improve the dissolution rate of poorly water soluble drugs.
- Bioavailability of poorly bioavailable drugs can be enhanced through liquisolid technology.
- Liquisolid formulations show better wettability.
- Liquisolid technology has also capability to slow down the drug release.
- Zero order release kinetics is achievable with liquisolid formulations.
- The retardation effect of hydroxypropylmethylcellulose is amplified in liquisolid formulations.
- The technology is in the early stages of its development with extensive research currently focused on.
- It is envisaged that the liquisolid compacts could play a major role in the next generation of tablets.

This box summarizes key points contained in the article.

lead to unsatisfactory results. For example, the use of polymorphs or pseudopolymorphs is often disappointing due to lack of stability. The liquisolid technique has been proven to be a very promising approach to obtain fast release formulations. This technology has also the capability to slow down drug release of highly water soluble drugs from tablet matrices provided the right excipient is selected. The application of the liquisolid technology in both areas (dissolution enhancement and sustained release action) is discussed extensively below.

Briefly, liquisolid systems are considered as free-flowing and compressible or compactable powders containing a non-volatile liquid vehicle and solid drug particles. The solid drug particles can be dissolved or partly dissolved by the liquid vehicle (co-solvent). This liquid system may be converted into a dry-looking, free-flowing and compressible powder by mixing with suitable excipients termed the carrier and coating materials, which is discussed later. In liquisolid formulations, the excipient with a capability to adsorb liquid on its surfaces is called the carrier which usually has the highest contribution in the formulation. The excipient with very high surface area which usually covers the carrier surfaces containing liquid to improve flowability of liquisolid powders is known as coating materials. The outline of liquisolid preparation is presented in **Figure 1**.

2. Theory of liquisolid systems

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials), a mathematical approach for the formulation of liquisolid systems has been developed by Spireas and Sadu [4,5]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder–liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk (w/w) while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression [6]. The compactability may be determined by the so-called 'pactisity' [4,6] which describes the maximum (plateau) crushing strength of a 1 g tablet compacted at sufficiently high compression forces.

The terms 'acceptable flow' and 'acceptable compression properties' imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate, an acceptably flowing and acceptably compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid:carrier ratio is termed 'liquid load factor L_f' (w/w) and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$L_f = W/Q \tag{1}$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q/q \tag{2}$$

The liquid load factor that ensures acceptable flowability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \Phi + \phi \cdot (1/R) \tag{3}$$

where Φ and ϕ are the Φ-values of the carrier and coating material, respectively.

Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R) \tag{4}$$

where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In **Table 1**, examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed.

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquisolid systems is equal to either $^{\Phi}L_f$ or $^{\Psi}L_f$, whichever represents the lower value.

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and coating (q_o) material required to convert a given amount

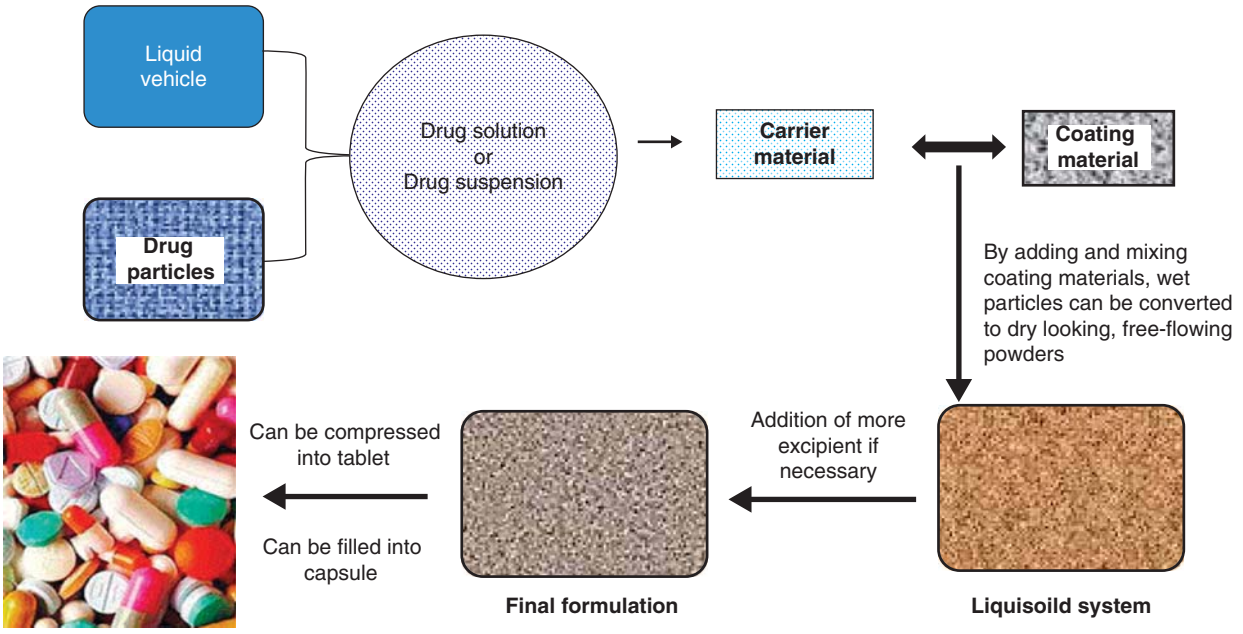

Figure 1. Outline of liquisolid preparation.

Table 1. Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles [4].

Powder excipient or system	Φ-Values		Ψ-Numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH 102	0.16	0.005	0.224	0.242
Avicel PH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (silica)* with Avicel PH 102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (silica)* with Avicel PH 200	2.57	2.44	0.712	0.717

*Included as coating material in carrier/coating powder systems.

of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q_o = W/L_o \quad (5)$$

and

$$q_0 = Q_o/R \quad (6)$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow [7] and compaction properties [4].

3. Liquisolid formulations as a tool to enhance drug release

Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems (**Table 2**).

3.1 Mechanisms of enhanced drug release from liquisolid systems

In the literature, several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, increased solubility of the drug and improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements [8-10].

3.1.1 Increased drug surface area

Even if the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is still located in the powder substrate in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets [5,10-13].

Accordingly, with increasing drug content exceeding the solubility limit and thus increasing fraction of undissolved

Table 2. Formulations of liquisolid systems with enhanced drug release.

Drug	Liquid vehicle	Carrier & coating material	Ref.
Aceclofenac	PEG 400	MCC & HPMC	[14]
Bromhexine HCl	PG	MCC & colloidal silica	[18]
Carbamazepine	PEG 200	MCC & colloidal silica	[8]
Clofibrate (liquid)	–	MCC & colloidal silica	[4]
Famotidine	PG	MCC & colloidal silica	[42]
Fenofibrate	PEG 400	MCC & colloidal silica	[15]
Fenofibrate	PG	MCC & colloidal silica	[79,80]
Furosemide	Synperonic® PE/L 81	MCC & colloidal silica	[19]
Glibenclamide	PEG 400	Colloidal silica & MCC	[81]
Griseofulvin	PEG 400	MCC & colloidal silica	[15]
Hydrochlorothiazide	PEG 200	MCC + magnesium carbonate & colloidal silica	[22]
Hydrocortisone	PG	MCC & colloidal silica	[4,11]
Hydrocortisone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various silicas*	[82]
Ibuprofen	PEG 300	MCC & colloidal silica	[83]
Indomethacin	PG	MCC & colloidal silica	[9,12]
Indomethacin	PEG 400	MCC & HPMC	[16]
Lamotrigin	PEG 400	MCC & colloidal silica	[15]
Methyclothiazide	PEG 400	MCC & colloidal silica	[4,23]
Naproxen	Cremophor® EL	MCC & colloidal silica	[28]
Piroxicam	Polysorbate 80	MCC & colloidal silica	[10,13]
Piroxicam	PG	MCC & colloidal silica	[27]
Polythiazide	PEG 400	MCC & colloidal silica	[26]
Prednisolone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various silicas*	[82]
Prednisolone	PG	MCC & colloidal silica	[5]
Prednisone	PG	MCC & colloidal silica	[4]
Prednisone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various silicas*	[82]
Repaglinide	Polysorbate 80	MCC & calcium silicate	[48]

*Drug solution dispersed on various silicas (no compacts).
Cremophor® EL: Polyoxyl 35 castor oil; HPMC: Hydroxypropylmethylcellulose; MCC: Microcrystalline cellulose; PG: Propylene glycol; Synperonic® PE/L 81: Polyoxyethylene-polyoxypropylene block copolymer.

drug in the liquid vehicle the release rate decreases. With various drugs, it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (F_M) in the liquid formulation [5,11-13]. F_M is defined by Spireas *et al.* as the ratio between the drug's solubility (S_d) in the liquid vehicle and the actual drug concentration (C_d) in this vehicle carried by each system [11].

Therefore:

$$F_M = S_d/C_d \quad (7)$$

where $F_M = 1$ if $S_d \geq C_d$.

In **Figure 2**, the effect of the fraction of the molecularly dispersed drug (F_M) on the release rate of hydrocortisone formulated as liquisolid compacts containing various drug concentrations in varying amounts of propylene glycol as liquid vehicle is shown. It is obvious that the drug release rate increases linearly with increasing F_M. Interestingly, this linear increase may be observed only above a certain F_M limit. Accordingly, lower F_M values and higher fraction of undissolved drug in the liquid vehicle, respectively, are not sufficient to increase percentage of drug released at 30 min. However, this may not be transferred to other time points of drug release.

3.1.2 *Increased drug solubility*

In addition to the first mechanism of drug release enhancement, it is expected that C_s, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid–liquid interface between an individual liquisolid primary particle and the release medium, it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the solubility of the drug if the liquid vehicle acts as a co-solvent [5,10-13]. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed by Yadav *et al.* [14-17].

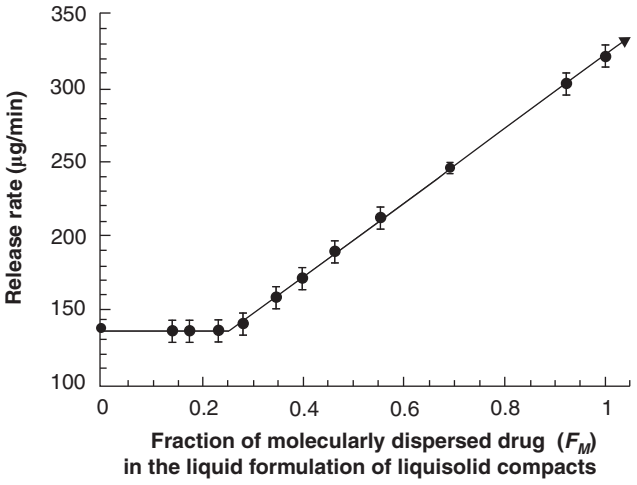

Figure 2. Effect of the fraction of molecularly dispersed drug (F_M) on the hydrocortisone release rate at 30 min of liquisolid compacts (means ± s.d., n = 3).
Adapted from [11].

3.1.3 *Improved wetting properties*

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles [10] and water rising times [14-16]. It is obvious from **Figure 3** that liquisolid compacts show lower contact angles compared to conventional tablets due to the presence of a surface active agent, for example, polysorbate 80 [10].

3.2 Optimization of liquisolid formulations with enhanced drug release

The liquisolid technique has been successfully applied to low dose poorly water soluble drugs. The formulation of a high dose poorly soluble drug is one of the limitations of the liquisolid technique. As the release rates are directly proportional to the fraction of molecularly dispersed drug (F_M) in the liquid formulation, a higher drug dose requires higher liquid amounts for a desired release profile. Moreover, to obtain liquisolid systems with acceptable flowability and compactability, high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the liquisolid technique, several formulation parameters may be optimized (**Table 3**).

In various studies, the effect of different types of nonvolatile liquid vehicles has been investigated. The results suggest that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus an increased F_M, leads to enhanced release profiles [5,12,18,19]. That means that by selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus the weight and size of the liquisolid tablets can be reduced. However, in addition to the drug solubility in the liquid vehicle, other physicochemical characteristics of the liquid vehicles such as polarity, viscosity, molecular mass, chemical structure and lipophilicity may also have an effect on drug release [5].

A further approach to minimize tablet weight is to increase the liquid load factor by using carrier and coating materials with a high specific surface area or by adding polyvinylpyrrolidone (PVP) to the liquid formulation. It was found that the higher the specific surface area of an excipient, the higher the liquid load factor [7]. For instance, the liquid adsorption capacity of microcrystalline cellulose (1.18 m^2/g) is higher than that of lactose (0.35 m^2/g), starch (0.6 m^2/g) and sorbitol (0.37 m^2/g) [10]. Fujicalin® (30 m^2/g), a spherically granulated dicalcium phosphate anhydrous, and Neusilin® US2 (300 m^2/g), a magnesium aluminometasilicate, turned out to be very effective excipients for liquid adsorption while maintaining acceptable flow and compaction properties [20,21].

Khaled [22] noticed precipitation and consequently retention of the drug in the cavities of porous excipients on contact of the liquid formulation with the release medium. This retention could be minimized by using either a dilute drug solution or PVP as crystallization inhibitor [8,22]. Moreover, PVP may also act as binder during compaction leading to an increase of the liquid load factor [8].

The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. It was found that the release rate increases by addition of super-disintegrants such as sodium starch glycolate or croscarmellose sodium to the liquisolid formulation [14-16].

Another formulation parameter that may be optimized is the ratio of carrier:coating material (R). An increase in the R-value results in an enhanced release rate if microcrystalline cellulose and silica are used as carrier and coating materials, respectively. Liquisolid tablets with high R-values contain high amounts of microcrystalline cellulose, low quantities of silica and low liquid:powder ratios. This is associated with enhanced wicking, disintegration and thus drug release. In contrast, if high amounts of silica are used, which means that the R-value is low, the liquisolid tablet is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/recrystallization of the drug and thus decreased release rates [8,23]. Moreover, as silica is a hydrophobic material high amounts of it can cause retardation of drug release. Therefore, Spireas *et al.* recommend a minimum R-value of 20 [23]. In the case of liquisolid sustained release tablets lower R-values may be used [24,25], which is discussed later.

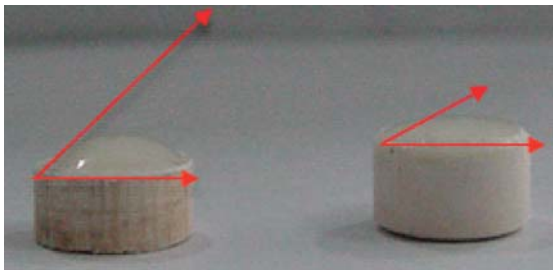

Figure 3. Better wettability of liquisolid tablets (unpublished data).

3.3 Stability of liquisolid systems with enhanced drug release

To obtain information on the stability of liquisolid systems, the effects of storage on the release profile and the crushing strength of liquisolid tablets were investigated. Stability studies of liquisolid systems containing polythiazide (40°C/42 and 75% r.h., 12 weeks) [26], hydrocortisone (ambient conditions, 10 months) [4], carbamazepine (25°C/75% r.h., 6 months) [8], indomethacin (25°C/75% r.h., 12 months) [9], piroxicam (25°C/75% r.h., 6 and 9 months, respectively) [10,27] or naproxen (20°C/76% r.h., 4 weeks) [28] showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of liquisolid tablets. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

4. Liquisolid formulations as a tool to prolong drug release

As the excipients (polymeric materials) used in the design of liquisolid tablets are similar to those used in the design of simple sustained release matrix tablets, a brief background on sustained release matrix tablets is beneficial for the reader.

4.1 Background

Extended release dosage forms, unlike conventional dosage forms, do not disintegrate and are formulated in such manner as to make the contained drug available over an extended period of time following administration. Theoretically, an oral sustained release matrix should allow a reduction in dosing frequency as compared to a conventional dosage form [29].

In the last 2 decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance [30]. Preparation of drug-embedded matrix tablets that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. Matrix systems are commonly used as sustained release dosage forms because it makes manufacturing easy [31]. There are lots of polymeric materials that have been explored as retarding agent in matrix systems and each of which presents a different approach to the matrix concept. Generally, these matrices for oral delivery can be assigned to one of the following groups. Although there has been much basic research devoted to the development of the following types of devices and much experimentation under idealized conditions that suggests that they will work, there are complications that can arise if the device is ingested orally [32].

4.1.1 *Fatty matrices (digestible base)*

These matrices are prepared by adding the drug and excipients to the molten fat or wax, congealing, granulating and compression into cores. Substances which produce these matrices include carnauba wax, fatty alcohol, glycerol palmitostearate, stearyl alcohol, beeswax, aluminum monostearate and glycerol monostearate [33]. On the one hand, the mechanism of drug release from these matrices can be diffusion of the drug through solvent-filled pores. On the other, they are potentially erodible and control the release of drug through a combination of diffusion and erosion.

4.1.2 *Plastic or inert matrices (non-digestible base)*

Plastic or inert matrices are prepared in a similar way to fatty matrices. Drug release from these matrices occurs by simple diffusion through water-filled pores. Water penetration into the matrix is the rate-limiting step in such systems unless channeling agents such as PEG are used. Water penetrates into the matrix and the drug is able to diffuse through these same pores leaving a matrix skeleton. Examples of polymers used to prepare this type of matrix are polyethylene, methylacrylate, methylmethacrylate, ethylcellulose, polyvinyl chloride and polyvinyl acetate.

4.1.3 *Hydrophilic matrices*

Hydrophilic polymers were first introduced as a potential candidate for sustained release in 1966 [34]. These are probably the cheapest and easiest matrices to prepare. The ingredients can be either directly compressed or granulated to aid flow. Once in contact with water, hydrophilic polymers hydrate forming a gel layer. The mechanism of drug release from hydrophilic matrices is a combination of drug diffusion and erosion [35]. Polymers used in the manufacture of hydrophilic matrices include:

i) Cellulose derivatives such as methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, hydroxymethylcellulose and hydroxypropylcellulose
ii) Non-cellulose polysaccharides of natural origin such as guar gum, alginates and carrageenan
iii) Acrylic acid polymers such as polyacrylamide and polymethacrylamide.

Table 3. Optimization of formulation parameters for liquisolid systems with fast drug release.

Formulation parameter	Optimization	Effect
Liquid vehicle	High drug solubility in the vehicle	Increased fraction of the molecularly dispersed drug (F_M)
Carrier and coating materials	High specific surface area	Increased liquid load factor (L_f)
Addition of excipients	Polyvinylpyrrolidone	Increased liquid load factor (L_f), increased viscosity of liquid vehicle, inhibition of precipitation
	Super-disintegrant	Fast disintegration
Excipient ratio (*R*)	High *R*-value	Fast disintegration, inhibition of precipitation

Although polymeric matrices can highly differ from each other due to the chemical and physical properties of the polymer (neutral, polyelectrolyte, liphophilic, hydrophilic or amphiphilic), they share the same structural characteristics [36,37].

Clearly, the choice of the polymer depends on the final route of administration (examples include oral, ophthalmic, rectal, vaginal and subcutaneous) and on different factors such as degree of matrix swelling, biodiversity, biocompatibility, interactions with drug, excipients and mechanical properties.

The use of HPMC-15 cps as matrix material in a direct compression process has been reported previously [38,39]. Hydroxypropylmethylcellulose (HPMC) is the excipient chosen by most formulators for the preparation of hydrophilic matrix systems most probably because of its fast gel formation resulting in fast initial release, and the formation of strong, viscous gels to prolong drug release [40].

4.2 Sustained release with liquisolid formulations

Although there are a few techniques to produce slow release formulations, the liquisolid technique is fairly new and a promising technique to provide a slow release pattern with zero order release kinetics [24,25,41]. The liquisolid technique as a new and promising method alters the dissolution rate of drugs. The technique has recently been used to enhance the dissolution rate of poorly water soluble drugs such as indomethacine, piroxicam, hydrocortisone, prednisolone, famotidine, naproxen and carbamazepine [5,7,8,12,28,42] as described earlier in this manuscript.

Simplicity, low cost and capability of industrial production are some of the advantages of the liquisolid approach to be used in liquisolid sustained release systems.

In order for liquisolid formulations to produce better sustained release performance, the surface area of liquisolid powders should be reduced by converting the powder into tablet form. This emphasizes that this type of formulations should be free flowing, able to form stable compacts at low compaction pressures (good compactibility) and should not stick to the punches.

Spireas and Bolton [41] were pioneers in this technology who presented the first information on liquisolid sustained release formulations in 1998. Until 2008, there were no systematic studies on the use of the liquisolid technique for controlling drug release from polymeric matrices. Capability of this technique to slow down the release of propranolol HCl and theophylline was extensively studied by Javadzadeh *et al.* [24] and Nokhodchi *et al.* [25] in 2008 and 2010, respectively.

The hypothesis behind the liquisolid technology to prolong drug release is that if hydrophobic carriers such as Eudragit® RL and RS are used instead of hydrophilic carriers, sustained release systems can be obtained. The presence of hydrophilic HPMC polymer grades amplifies the retardation effect of this technology [25]. In addition, in liquisolid sustained release formulation, usually the surface area of carrier (Eudragit RS or RL) is low compared to the carriers used in fast release liquisolid formulation (Avicel); therefore, in order to increase loading factor and obtain a better flowability the amount of coating material (silica) is usually high [24]. This in turn helps to induce more retardation properties to the liquisolid formulations as silica is a hydrophobic material.

Although the technology might look very easy to apply to drugs with different solubilities, it seems that the industrial application of the liquisolid technique can be hampered due to a few hurdles such as poor flowability and poor compactibility of the liquisolid powder blend. Recently, the flowability of liquisolid powder blends was addressed by the application of a new mathematical model which is described earlier in this manuscript. This new mathematical model enables formulators to calculate the appropriate quantities of carriers or excipients required to prepare acceptably flowing powders. However, the high weight of sustained release liquisolid tablets represents a problem as the amount of drug is generally higher than in conventional tablets. Moreover, in order for tablets to retain their integrity they should be robust compacts and not disintegrate easily in the dissolution medium. Otherwise, the retardation effect might be suppressed. These shortfalls can be overcome by increasing the percentage of adjuvant in the formulations; however, this leads to a final weight of the tablets > 1 g which makes them difficult to swallow. Thus, in practice it is relatively difficult to convert conventional tablet formulations containing a high amount of drug or liquid drug such as clofibrate to liquisolid compacts with the same final tablet weight as the conventional tablets. One

approach to reduce the tablet weight is the incorporation of highly compactable excipients such as microcrystalline cellulose in liquisolid formulations. However, it has been reported that the compression of these liquisolid formulations containing liquid drugs might lead to a considerable liquid squeezing out from the compacts [4].

A recent approach was introduced by Javadzadeh *et al.* [8] stating that an increase in the loading factor could reduce the amount of carrier and coating materials to be added in liquisolid formulations and still to obtain acceptable flowability and compactibility for liquisolid powders. They showed that by incorporation of hydrophilic polymers such as PVP, HPMC and PEG 35000, the loading factor can be increased [8]. The authors used these hydrophilic polymers to reduce the final tablet weight with the highly dosed drug carbamazepine. They believed that by adding PVP to the liquid system (microsystems), it would be possible to produce dry powder formulations containing liquid with a high concentration of drug. By addition of such materials to the liquid system, a low amount of carrier is required to obtain a dry powder with free flowability and good compactibility. The authors believe that by preparing microsystems (adding some additives such as PVP, HPMC or PEG 35000 to the liquid system), the loading factor can be increased above 0.25. The results showed that the loading factor for carbamazepine powder blends containing microcrystalline cellulose as carrier and PEG 35000 as hydrophilic polymer can indeed be increased to 0.6 and still these formulations possess good flow properties. Similar results were obtained with sustained release liquisolid formulations of theophylline where the loading factor was around 0.66 and they still showed better flowability than their physical mixtures (**Table 4**). This could be attributed to the granulating effect of the co-solvents used in the formulation of the liquisolids. In addition, the liquid vehicle containing the drug can initially be adsorbed by the carrier surface followed by covering the carrier surface with the fine coating particles (silica) to yield granules with high flowability. As the physical mixtures contained very fine particles, they could not flow very well due to large cohesive or adhesive forces as a result of the high surface area of the fine particles.

The data presented in **Table 4** show that in most cases the liquisolid compacts are superior to the physical mixtures in terms of tablet hardness. For example, liquisolid compacts containing silica:Eudragit RL at a ratio of 1:1 showed a higher hardness (173 N) than their physical mixture counterparts (37 N). On the other hand, liquisolid compacts containing PEG 200 showed a lower hardness than its physical mixture. This indicates that the type of liquid vehicle, ratio of silica: Eudragit, type of Eudragit and presence of HPMC could have a remarkable effect on the mechanical properties of liquisolid tablets. It can be concluded that not only all of the liquisolid formulations have better flowability than the physical mixtures but also some of them showed better compactibility than the physical mixtures.

Regarding the selection of the type of liquid vehicle for sustained release action in liquisolid formulations, it was suggested that the liquid vehicle with less capability to dissolve the drug can be selected to obtain a better retardation effect. This is in contrast to fast release liquisolid formulations where a liquid vehicle with a high capability to dissolve the drug should be selected. For example, propranolol HCl (a highly water soluble drug) and theophylline (low solubility in water) both showed the lowest solubility in polysorbate 80 (**Table 5**) and this liquid vehicle was incorporated in liquisolid sustained release formulations of propranolol HCl and theophylline. This does not mean that the other liquid vehicles cannot be used in liquisolid formulations because Nokhodchi *et al.* [25] showed that other liquid vehicles listed in **Table 5** can be used to obtain sustained release liquisolid formulations (**Figure 4**).

It was shown that the drug solubility also has a significant effect on the performance of liquisolid compacts to provide sustained release properties. In the case of propranolol HCl formulations containing Eudragit RL or RS, liquisolid tablets showed slower release rates than their conventional counterpart tablets [24] whereas with theophylline there were no significant ($p > 0.05$) differences between some of the liquisolid tablets and the conventional dosage forms [25]. This could be due to the different solubility of the two drugs as the only difference between these two studies was the difference in drug solubility (solubility of propranolol HCl was about 750 mg/ml, whereas solubility of theophylline was 12 mg/ml at pH 6.5). This indicates that the liquisolid technique can prolong drug release from liquisolid compacts even if highly water soluble drugs are incorporated in their liquid formulations.

Javadzadeh *et al.* [24] stated that polysorbate 80 (Tween 80) plays an important role in sustaining drug release from liquisolid matrices, and that a reduction of the glass transition temperature (T_g) of Eudragit RL or RS can be the reason for the release prolongation of liquisolid tablets in the presence of polysorbate 80. This was further explained by Gruetzmann and Wagner [43] by a plasticizer effect of polysorbate 80 which leads to a reduction of the glass transition temperature and thus a higher flexibility of the polymer chains. Plasticizers affect the intermolecular bonding between polymer chains, thereby, increasing flexibility [44]. Therefore, reduction of the T_g of the polymer might be the reason for the release prolongation of liquisolid tablets. At a temperature above the T_g a better coalescence of the polymer particles occurs forming a fine network and a matrix with lower porosity and higher tortuosity. This way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug [45]. It has been shown that the T_g of Eudragit RL in the liquisolid formulation was 44 ± 2°C whereas in the physical mixture without polysorbate 80 the T_g was 63 ± 3°C. When Eudragit polymers were mixed with Tween 80 (the final concentration of Tween 80 to Eudragit was 30% w/w), the T_g of the sample was reduced

Table 4. Flow and mechanical properties of liquisolid formulations and their physical mixture counterparts.

	Formulation	Carr index (%)*		Hardness (N)	
		Liquisolid powder	Physical mixture	Liquisolid compact	Physical mixture
F1	LS-Silica:Eud.RL (1:1) Tween 80	8.89 ± 0.57	23.71 ± 0.33	173 ± 7	37 ± 1
F2	LS-Silica:Eud.RL (1:2) Tween 80	11.93 ± 0.26	24.36 ± 0.13	65 ± 1	72 ± 1
F3	LS-Silica:Eud.RL (1:3) Tween 80	12.03 ± 0.11	23.20 ± 0.60	60 ± 1	77 ± 1
F4	LS-Silica:Eud.RL (1:4) Tween 80	10.44 ± 0.43	24.56 ± 0.40	79 ± 8	79 ± 2
F5	LS-Silica:Eud.RS (1:1) Tween 80	14.79 ± 0.32	26.31 ± 0.37	150 ± 3	43 ± 1
F6	LS-Silica:Eud.RS (1:2) Tween 80	12.17 ± 0.80	27.37 ± 0.21	65 ± 3	21 ± 1
F7	LS-Silica:Eud.RS (1:3) Tween 80	11.51 ± 0.23	21.91 ± 1.21	63 ± 1	37 ± 1
F8	LS-Silica:Eud.RS (1:4) Tween 80	10.53 ± 0.30	22.32 ± 0.39	66 ± 1	53 ± 1
F9	LS-Silica: Eud.RL (1:2) PEG200	12.21 ± 0.38	24.36 ± 0.13	28 ± 2	72 ± 1
F10	LS-Silica: Eud.RL (1:2) PEG 600	9.65 ± 0.40	24.36 ± 0.13	2 ± 1	72 ± 1
F11	LS-Silica:Eud.RL (1:2) Tween 20	10.98 ± 0.66	24.36 ± 0.13	70 ± 2	72 ± 1
F12	LS-Silica: Eud.RL (1:2) PG	15.27 ± 0.38	24.36 ± 0.13	48 ± 2	72 ± 1
F13	F4 + 6% HPMC E4M	12.70 ± 0.18	19.87 ± 0.66	67 ± 3	59 ± 1
F14	F4 + 10% HPMC E4M	12.27 ± 0.08	24.47 ± 0.52	69 ± 2	44 ± 1
F15	F4 + 15% HPMC E4M	13.60 ± 0.21	22.76 ± 0.25	93 ± 5	42 ± 1
F16	F10 + 10% HPMC E4M	12.60 ± 0.30	24.47 ± 0.52	22 ± 1	44 ± 1
F17	F12 + 10% HPMC E4M	13.46 ± 0.36	24.47 ± 0.52	58 ± 1	44 ± 1
F18	F4 + PVP K30 10%	13.64 ± 0.58	20.43 ± 0.39	64 ± 2	83 ± 2
F19	F4 + PVP SR 10%	12.45 ± 0.28	21.10 ± 0.59	79 ± 1	48 ± 1

*Carr index below 15 is an indication of good flow (data taken from [25]).
HPMC: Hydroxypropylmethylcellulose; PG: Propylene glycol; PVP: Polyvinylpyrrolidone.

Table 5. Solubility of theophylline and propranolol HCl in different liquid vehicles.

Liquid vehicle	Theophylline solubility (mg/ml)	Propranolol HCl solubility (mg/ml)
PEG 600	14.5	–
PEG 400	–	79.7
PEG 200	17	79.3
Glycerine	–	39.1
Propylene glycol	14.11	102.9
Polysorbate 80	11.26	13.3

Data taken from [24,25].

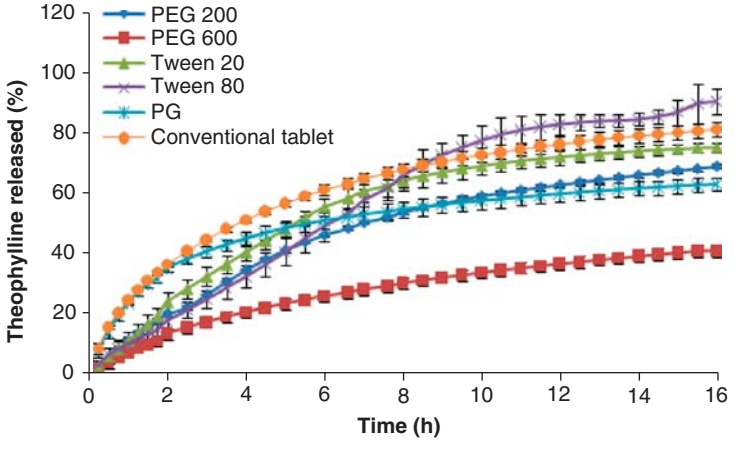

Figure 4. The effect of the type of liquid vehicle on the release of theophylline from liquisolid compacts containing Eudragit RL as carrier.
Figure taken from [25].

to 15°C which is well below the temperature of manufacturing process [43]. This in turn can improve the coalescence of the polymers before adding other ingredients to the mixtures of polymer and liquid medication (Tween 80 plus drug). This indicates that the presence of other ingredients in liquisolid formulation increases the T_g of the final formulation.

One of the main advantages of liquisolid compacts is the possibility of achieving a zero order release pattern. The release data for all formulations listed in **Table 4** were subjected to the Peppas equation $Q = kt^n$ where Q is the amount of drug release (%) at time t, k is the drug release constant and n is the release exponent which is an indicator of the mechanism of drug release. In case of cylindrical tablets when n approximates 0.45, a Fickian/diffusion-controlled drug release is implied, if the value of n approaches 0.89; phenomenologically one may conclude that the release is approaching zero order release (erosion mechanism). It was interesting to note that all formulations containing Tween 80 (formulations F1 to F8 in **Table 4**) showed higher n values than the physical mixtures. The n values for these liquisolid tablets varied between 0.58 and 0.99 whereas the n values for the physical mixtures were between 0.34 and 0.60. This indicates that the contribution of erosion in liquisolid tablets is higher than the contribution of the diffusion mechanism. These data also indicated that some of the liquisolid compacts showed near zero order release kinetics such as formulations F2, F5, F6 and F16 listed in **Table 4**. Gonjari *et al.* [46] used the liquisolid technology to prepare tramadol HCl liquisolid compacts using propylene glycol as the liquid vehicle (solubility of tramadol HCl was 6.25 g/10 ml), HPMC K4M as a retardant agent and Avicel® PH 102 as the carrier. In these liquisolid compacts between 100 and 200 mg HPMC K4M were used and the results showed that the amount of HPMC had no significant effect on drug release. This was in contrast to the results obtained by Nokhodchi *et al.* [25] who showed that an increase in HPMC concentration from 6 to 15% resulted in a remarkable reduction in the release rate of theophylline (**Figure 5**). This might be explained by the presence of either Eudragit RS 100 or Tween 80 (polysorbate 80) in theopylline liquisolid compacts. On the other hand, liquisolid compacts containing Avicel PH 102 should disintegrate as Avicel has disintegrating properties which can facilitate the dissolution rate. Comparing these three studies showed that the selection of liquid vehicle, retardant agent as well as carrier and coating material for formulating liquisolid compacts for sustained release purposes are crucial.

5. *In vivo* consideration of liquisolid systems

Khaled *et al.* [47] studied the clinical profiles of hydrochlorothiazide liquisolid tablets in six male beagle dogs for the first time in 2001. They concluded that there were significant differences between the two formulations mentioned in **Table 6** with regard to $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$ and C_{max}. Their findings showed an increase in the bioavailability of the drug by 15% when formulated as liquisolid tablets. However, no significant difference was observed between commercial hydrochlorothiazide tablets and its liquisolid formulations with regard to the rate of absorption. Similar conclusions were made by El-Houssieny *et al.* [48] where repaglinide liquisolid formulations showed a better bioavailability than its commercial product (**Table 6**). In another study, six healthy male volunteers aged between 20 and 40 years were tested with regard to differences between commercial famotidine tablets and its liquisolid compacts [42]. The authors pointed out that there was no significant difference between the commercial tablet and the liquisolid tablets in terms of pharmacokinetic parameters.

These contradictory conclusions made by different authors on the performance of liquisolid formulations could be due to a difference in the solubility of famotidine, hydrochlorothiazide and repaglinide in their liquid vehicles used (in case of famotidine propylene glycol was used whereas in case of hydrochlorothiazide and repaglinide PEG 200 and polysorbate 80 were used, respectively). These contrary results on liquisolid formulations showed that still more *in vivo* data are needed to confirm the superiority of the liquisolid tablets. However, generally, most studies showed better performance of liquisolid formulations compared to their commercial products (**Table 6**).

6. Brief comparison between immediate release liquisolid systems and alternative technologies

The liquisolid technique is a promising technique because of the simple manufacturing process, low production costs and the possibility of industrial production due to good flow and compaction properties of the liquisolid formulations.

In the next subsection, the liquisolid technique is compared to alternative technologies for the enhancement of drug release and their advantages and disadvantages are pointed out.

6.1 Technologies for the enhancement of drug release

Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility or by formulating the drug in its dissolved state. Several methodologies such as micronization, adsorption onto high surface area carriers, co-grinding, formulation of inclusion complexes, solid dispersions and lipid-based formulations (e.g., SEDDS) are used for enhancement of drug release [49-51].

Micronization can be carried out by using various mills to increase the surface area of drugs and the main advantage of this technique is its simplicity [52]. However, in practice the effect of micronization is often disappointing, especially if the drugs are encapsulated or tableted. Micronized drugs have the tendency to aggregate as a result of their hydrophobicity and electrostatic charge, thus reducing their available surface area [53,54].

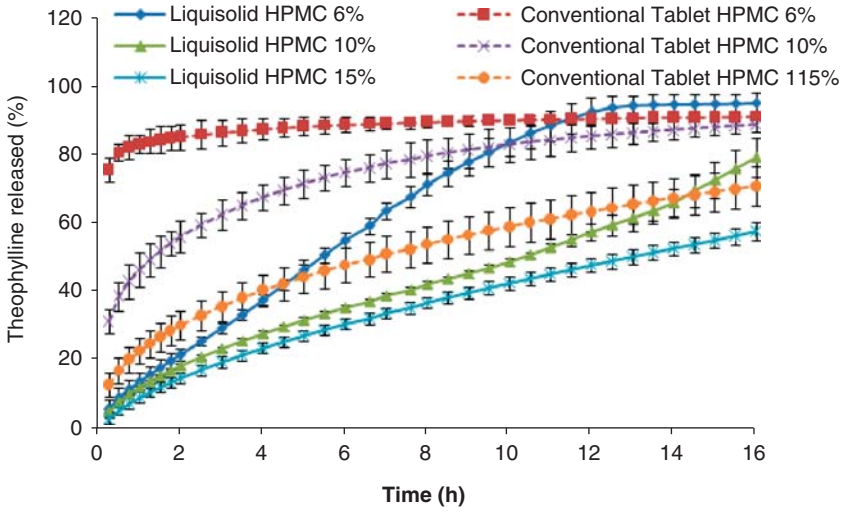

Figure 5. The effect of HPMC concentration on drug release from liquisolid compacts and conventional sustained release tablets.

Figure taken from [25].

HPMC: Hydroxypropylmethylcellulose.

Table 6. Mean bioavailability and pharmacokinetic parameters of liquisolid formulations following the administration of a single oral dose (25 mg hydrochlorothiazide, 2 mg repaglinide) compared to the commercial formulation.

Pharmacokinetic parameter	Hydrochlorothiazide*			Repaglinide‡		
	Commercial	Liquisolid	p-Value	Commercial	Liquisolid	p-Value
C_{max} (ng/ml)	734 ± 116	970 ± 161	0.0252	70 ± 5	125 ± 3	< 0.0001
t_{max} (h)	2.4 ± 0.9	2.1 ± 0.7	0.3939	1 ± 0	1 ± 0	1.0
$AUC_{0\rightarrow t}$ (ng·h/ml)	4692 ± 1333	5622 ± 1039	0.0363	190 ± 3	374 ± 2	< 0.0001
$AUC_{0\rightarrow\infty}$ (ng·h/ml)	5435 ± 1627	6373 ± 1201	0.0124	227 ± 3	471 ± 1	< 0.0001

Data taken from [47,48].

*Beagle dogs, n = 6.

‡Rabbits, n = 12.

Adsorption of poorly soluble drugs on hydrophilic silica aerogels was found to enhance drug dissolution. This can be explained by both an increase in the specific surface area of the drug adsorbed to the aerogel and an at least partial amorphization of the drug. The main advantage with hydrophilic aerogels as drug carriers is that this type of formulation really promotes the very fast release of drugs [55] even better than nanoparticles [56]. Furthermore, as the drug particles are being adsorbed or crystallized in the solid aerogel matrix, thus, they have a lower tendency to agglomerate and are better protected from the environment compared to nanoparticles. However, drug adsorption is dependent on the selected drug and sometimes only low drug loads are achieved. Another disadvantage of this technique is the complex manufacturing process: silica aerogels are loaded with drugs by adsorption from their solutions in supercritical carbon dioxide [57,58].

Co-grinding of poorly soluble drugs with different excipients may also result in an amorphization of the drug and thus improved dissolution. Crospovidone [59,60], PVP [60] and different types of silica [61,62] are suitable for this purpose. Co-grinding is another straight forward procedure to achieve drug release enhancement. Co-grinding technique is economically and environmentally desirable as, unlike other techniques, it does not require toxic solvents and sophisticated equipment. Therefore, recently, researchers paid a special attention to apply the technique on various poorly water soluble drugs [63-65].

Complexes of a lipophilic drug with cyclodextrin, commonly known as inclusion complexes, can be easily formulated by mixing the drug with the carrier. The most commonly used carrier β-cyclodextrin acts as a solubilizer and stabilizer consisting of a truncated cone type structure with an outer hydrophilic and an inner hydrophobic surface [66,67]. However, the maximum possible drug load of these systems is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule.

Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusion) or solvent method. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With the solvent method, drug and carrier are dissolved in small amounts of solvent with final solvent evaporation. The higher release rates of solid dispersions may be ascribed to a number of factors which include formation of the amorphous form of the drug, reduction of particle size to nearly the molecular level, improved wetting properties and solubilization of the drug by the carrier [67-73]. The advantages of this methodology are the molecular dispersion of the drug within the hydrophilic carrier and the comparably high drug stability. In addition, solid dispersion technique is the most promising method to formulators because of its ease of preparation, ease of optimization and reproducibility.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, co-solvent and drug, which emulsify spontaneously to produce oil in water emulsions when introduced into an aqueous phase under gentle agitation [74]. Generally, SEDDS are either administered as liquid dosage forms or as soft gelatin capsules. In general, solid dosage forms are preferred over liquid preparations for many reasons including ease of manufacture, patient compliance, dosage uniformity and stability. Liquid SEDDS may be transformed to solid self-emulsifying systems by addition of powder carriers [75-78]. The liquisolid technique may be used to transform liquid SEDDS into acceptably flowing and compressible powders. One of the drawbacks of this technique is the high surfactant concentration [49].

7. Conclusion

Poor water solubility is an issue of increasing gravity with the newly developed drugs shifted towards higher lipophilicities. Classic formulation strategies often fail to achieve the desired bioavailability for such drugs. The liquisolid technology has proven to be a useful innovative tool for improving the bioavailability by enhancing drug release. It is an effective technology in terms of production capability and low cost of formulations. Therefore, this technology has the potential for large scale manufacture. The present review also showed that the liquisolid technology can be used for the purpose of slowing down the drug release for highly water soluble drugs if the right excipients are selected.

8. Expert opinion

With the advent of high-throughput screening and combinatorial chemistry, it has been shown that most of the new chemical entities have a high lipophilicity and poor aqueous solubility, hence, poor bioavailability. In order to improve the bioavailability, the release rate of these drugs should be enhanced. Although there are multiple technologies to tackle this issue, they are not cost effective due to the involvement of sophisticated machinery, advanced preparation techniques and complicated technology. As the liquisolid technology uses a similar production process as the conventional tablets, this technology to improve the release rate of poorly water soluble drugs will be cost effective. Moreover, as the route of administration of this type of formulation is the oral route, the patient compliance for the final products obtained by the liquisolid technology will be high. This technology also has the capability to slow down drug release and allows preparing sustained release tablets with zero order drug release pattern. The excipients required for this technology are conventional and commonly available in the market. The technology is in the early stages of its development with extensive research currently focused on. It is envisaged that the liquisolid compacts could play a major role in the next generation of tablets.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lipiniski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development setting. Adv Drug Deliv Rev 1997;23:3-25
2. Lipiniski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods 2000;44:235-49
3. Liversidge EM. Nanocrystals: resolving pharmaceutical formulation issues associated with poorly water soluble compounds. In: Marty JJ, editor, Particles. Marcel Dekker, Orlando; 2002
4. Spireas S. Liquisolid systems and methods of preparing same. US6423339B1; 2002

•• **This article provides a comprehensive summary of the liquisolid technique.**

5. Spireas S, Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pharm 1998;166:1771-88
6. Grover R, Spireas S, Lau-Cam C. Development of a simple spectrophotometric method for propylene glycol detection in tablets. J Pharm Biomed Anal 1998;16:931-8
7. Spireas SS, Jarowski CI, Rohera BD. Powdered solution technology: principles and mechanism. Pharm Res 1992;9:1351-8

•• **This article introduces the application of solution technology in pharmaceutical formulations.**

8. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm 2007;341:26-34

• **This article shows how loading factor in liquisolid formulations can be increased without negative effect of the liquid medication on flow and compactibility of powders.**

9. Javadzadeh Y, Siahi MR, Asnaashari S, et al. Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties. Acta Pharm 2007;57:99-109
10. Javadzadeh Y, Siahi MR, Asnaashari S, et al. An investigation of physicochemical properties of piroxicam liquisolid compacts. Pharm Dev Technol 2007;12:337-43

• **In this paper, various parameters of the liquisolid technique are investigated and thoroughly explained.**

11. Spireas S, Sadu S, Grover R. In vitro release evaluation of hydrocortisone liquisolid tablets. J Pharm Sci 1998;87:867-72
12. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR, et al. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci 2005;8:18-25

• **This is the first comprehensive work on liquisolid technology after Spireas, *et al*. The article shows the main mechanism behind the dissolution enhancement of liquisolid formulations for poorly water soluble drugs.**

13. Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M, et al. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Farmaco 2005;60:361-5
14. Yadav VB, Nighute AB, Yadav AV, et al. Aceclofenac size enlargement by non aqueous granulation with improved solubility and dissolution. Arch Pharm Sci Res 2009;1:115-22
15. Yadav VB, Yadav AV. Enhancement of solubility and dissolution rate of BCS class II pharmaceuticals by nonaqueous granulation technique. Int J Pharm Res Dev 2010;1:1-12
16. Yadav VB, Yadav AV. Improvement of solubility and dissolution of indomethacin by liquisolid and compaction granulation technique. J Pharm Sci Res 2009;1:44-51
17. Yadav VB, Yadav AV. Liquisolid granulation technique for tablet manufacturing: an overview. J Pharm Res 2009;2:670-4
18. Gubbi S, Jarag R. Liquisolid technique for enhancement of dissolution properties of bromhexine hydrochloride. Res J Pharm Tech 2009;2:382-6
19. Akinlade B, Elkordy AA, Essa EA, et al. Liquisolid systems to improve the dissolution of furosemide. Sci Pharm 2010;78:325-44
20. Hentzschel CM, Sakmann A, Leopold CS. Flowability of liquisolid powder blends. AAPS Annual Meeting and Exposition; Atlanta; 2008
21. Hentzschel CM, Sakmann A, Leopold CS. Suitability of various tableting excipients as carriers for liquisolid systems. 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology; Malta; 2010
22. Khaled KA. Formulation and evaluation of hydrochlorothiazide liquisolid tablets. Saudi Pharm J 1998;6:39-46
23. Spireas S, Wang T, Grover R. Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid compacts. Drug Dev Ind Pharm 1999;25:163-8
24. Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm 2008;362:102-8

•• **This is the first comprehensive study on the application of liquisolid technology in controlled release formulations.**

25. Nokhodchi A, Aliakbar R, Desai S, Javadzadeh Y. Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release. Colloids Surf B Biointerfaces 2010;79:262-9

• **This article shows the possibility of achieving zero order release pattern with liquisolid compacts and also how the retardation effect of HPMC can be amplified.**

26. Sheth A, Jarowski CI. Use of powdered solutions to improve the dissolution rate of polythiazide tablets. Drug Dev Ind Pharm 1990;16:769-77
27. Javadzadeh Y, Shariati H, Movahhed-Danesh E, et al. Effect of some commercial grades of microcrystalline cellulose on flowability, compressibility, and dissolution profile of piroxicam liquisolid compacts. Drug Dev Ind Pharm 2009;35:243-51
28. Tiong N, Elkordy AA. Effects of liquisolid formulations on dissolution of naproxen. Eur J Pharm Biopharm 2009;73:373-84
29. Qiu Y, Zhang G. Research and development aspects of oral

controlled-release dosage forms in Handbook of Pharmaceutical Controlled Release Technology. In: Wise DL, editor, CRC, Inc.; 2000

30. Merkus FWHM. Controlled and rate-controlled drug delivery; principal characteristics, possibilities and limitations. In: Struyker-Boudier HAJ, editors, Rate- controlled drug administration and action. CRC Press, Boca Raton, FL, USA; 1986. p. 15-47
31. Cardinal JR. Matrix systems. In: Langer RS, Wise DL, editors, Medical applications of controlled release. Volume 1. Classes of systems. CRC Press, Boca Raton, FL, USA; 1984. p. 41-67
32. Ritschel WA. Influence of formulating factors on drug safety of time-release nitroglycerin tablets. J Pharm Sci 1971;60:1683-5
33. Ding X, Alani AWG, Robinson JR. Extended-release and targeted drug delivery systems in Remington – the science and practice of pharmacy. 21st edition. Lippincott Williams and Wilkins; 2005
34. Huber HE, Dale LB, Christensen GL. Utilization of hydrophilic gums for the control of drug release from tablet formulations. I. disintegration and dissolution behaviour. J Pharm Sci 1966;55:974-6
35. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. Int J Pharm Tech Prod Mfr 1984;5:1-9
36. Grassi M. PhD Thesis, VIII Ciclo, University of Trieste, Department of Chemical Engineering (DICAMP); 1996
37. Lapasin R, Pricl S. Rheology of industrial polysaccharides, theory and applications. Champman and Hall, London; 1995
38. Bain JC, Tan SB, Ganderton D, Solomon MS. Comparison of the in vitro release characteristics of a wax matrix and a hydrogel sustained release diclofenac sodium tablet. Drug Dev Ind Pharm 1991;17:215-32
39. Lee BJ, Ryu SG, Cui JH. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. Drug Dev Ind Pharm 1999;25:493-501
40. The Dow Chemical Company, Formulation for controlled release with Methocel cellulose ethers, USA; 1987
41. Spireas S, Bolton S. Sustained-release "liquisolid compacts". Int Symp Control Rel Bioact Mater 1998;25:138-9
42. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. Eur J Pharm Biopharm 2008;69:993-1003
43. Gruetzmann R, Wagner KG. Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from Eudragit RS films by differential scanning calorimetry. Eur J Pharm Biopharm 2005;60:159-62
44. Porter SC, Bruno HB. Coating of pharmaceutical solid-dosage forms. In: Lieberman HA, Lachman L, Schwartz JB, editors, Pharmaceutical dosage forms: tablets. Volume 3. 2nd edition. Marcel Dekker, Inc., New York; 1990
45. Azarmi S, Farid J, Nokhodchi A, et al. Thermal treatment as a tool for sustained release of indomethacin from Eudragit RS and RL matrices. Int J Pharm 2002;246:171-7
46. Gonjari ID, Karmarkar AB, Hosmani AH. Evaluation of in vitro dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets. Digest J Nanomaterials Biostructures 2009;4:651-61
47. Khaled KA, Asiri YA, El-Sayed YM. In vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs. Int J Pharm 2001;222:1-6

•• **This is the first study showing better bioavailability of liquisolid tablets compared to conventional tablets.**

48. El-Houssieny BM, Wahman LF, Arafa NMS. Bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits. Biosci Trends 2010;4:17-24
49. Sharma A, Jain CP. Techniques to enhance solubility of poorly soluble drugs: a review. J Global Pharm Technol 2010;2:18-28
50. Saharan VA, Kukkar V, Kataria M, et al. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. Int J Health Res 2009;2:107-24
51. Saharan VA, Kukkar V, Kataria M, et al. Dissolution enhancement of drugs. Part II: effect of carriers. Int J Health Res 2009;2:207-23
52. Kubo H, Osawa T, Takashima K, et al. Enhancement of oral bioavailability and pharmacological effect of 1-(3,4-dimethoxyphenyl)-2,3-bis (methoxycarbonyl)-4-hydroxy-6,7,8-trimeth oxynaphthalene (TA-7552), a new hypocholesterolemic agent, by micronization in co-ground mixture with D-mannitol. Biol Pharmacol Bull 1996;19:741-7
53. Lin SL, Menig J, Lachman L. Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water-insoluble drugs. J Pharm Sci 1968;57:2143-8
54. Aguiar AJ, Zelmer JE, Kinkel AW. Deaggregation behavior of a relatively insoluble substituted benzoic acid and its sodium salt. J Pharm Sci 1967;56:1243-52
55. Smirnova I, Suttirungwong S, Seiler M, Arlt W. Dissolution rate enhancement by adsorption of poorly soluble drugs on hydrophilic silica aerogels. Pharm Dev Technol 2004;9:443-52
56. Smirnova I, Arlt W. Synthesis of silica aerogels and their application as drug delivery system. Supercritical Fluids as Solvents and Reaction Media; 2004. p. 381-5
57. Smirnova I, Tuerk M, Wischumerski R, et al. Comparison of different methods for enhancing the dissolution rate of poorly soluble drugs: case of griseofulvin. Eng Life Sci 2005;5:277-80
58. Smirnova I, Suttiruengwong S, Arlt W. Feasibility study of hydrophilic and hydrophobic silica aerogels as drug delivery systems. J Non Cryst Solids 2004;350:54-60
59. Fujii M, Okada H, Shibata Y, et al. Preparation, characterization, and tableting of a solid dispersion of indomethacin with crospovidone. Int J Pharm 2005;293:145-53
60. Barzegar-Jalali M, Valizadeh H, Shadbad MRS, et al. Cogrinding as an approach to enhance dissolution rate of a poorly water-soluble drug (gliclazide). Powder Technol 2010;197:150-8

61. Bahl D, Bogner RH. Amorphization of indomethacin by co-grinding with Neusilin US2: amorphization kinetics, physical stability and mechanism. Pharm Res 2006;23:2317-25

62. Ali AS, Yamamoto K, Elsayed AM, et al. Molecular behavior of flufenamic acid in physical and ground mixtures with florite. Chem Pharm Bull 1992;40:1289-94

63. Al-Hamidi H, Edwards AA, Mohammad Amin M, Nokhodchi A. Glucosamine HCl as a new carrier for improved dissolution behaviour: effect of grinding. Colloids Surf B Biointerfaces 2010;81:96-109

64. Barzegar-Jalali M, Valizadeh H, Siahi Shadbad M, et al. Co-grinding as an approach to enhance dissolution rate of a poorly water-soluble drug (gliclazide). Powder Technol 2010;197:150-8

65. Vogt M, Kunath K, Dressman JB. Dissolution improvement of four poorly water soluble drugs by cogrinding with commonly used excipients. Eur J Pharm Biopharm 2008;68:330-7

66. Casella R, Williams DA, Jambhekar SS. Solid-state beta-cyclodextrin complexes containing indomethacin, ammonia and water. II. Solubility studies. Int J Pharm 1998;165:15-22

67. Ruan LP, Yu BY, Fu GM, et al. Improving the solubility of ampelopsin by solid dispersions and inclusion complexes. J Pharm Biomed Anal 2005;38:457-64

68. Barzegar-Jalali M, Dastmalchi S. Kinetic analysis of chlorpropamide dissolution from solid dispersions. Drug Dev Ind Pharm 2007;33:63-70

69. Valizadeh H, Zakeri-Milani P, Barzegar-Jalali M, et al. Preparation and characterization of solid dispersions of piroxicam with hydrophilic carriers. Drug Dev Ind Pharm 2007;33:45-56

70. Valizadeh H, Nokhodchi A, Qarakhani N, et al. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin and Eudragit® E100. Drug Dev Ind Pharm 2004;30:303-17

71. Verheyen S, Blaton N, Kinget R, et al. Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. Int J Pharm 2002;249:45-58

72. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002;231:131-44

73. Corrigan OI. Mechanisms of dissolution of fast release solid dispersions. Drug Dev Ind Pharm 1985;11:697-724

74. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci 2000;11:S93-8

75. Nazzal S, Nutan M, Palamakula A, et al. Optimization of a self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm 2002;240:103-14

76. Agarwal V, Siddiqui A, Ali H, et al. Dissolution and powder flow characterization of solid self-emulsified drug delivery system (SEDDS). Int J Pharm 2009;366:44-52

77. Bansal T, Mustafa G, Khan ZI, et al. Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs. Crit Rev Ther Drug Carrier Syst 2008;25:63-116

78. Mahmoud EA, Bendas ER, Mohamed MI. Preparation and evaluation of self-nanoemulsifying tablets of carvedilol. AAPS PharmSciTech 2009;10:183-92

79. Karmarkar AB, Gonjari ID, Hosmani AH, et al. Dissolution rate enhancement of fenofibrate using liquisolid tablet technique. Lat Am J Pharm 2009;28:219-25

80. Karmarkar AB, Gonjari ID, Hosmani AH, et al. Dissolution rate enhancement of fenofibrate using liquisolid tablet technique. Part II: evaluation of in vitro dissolution profile comparison methods. Lat Am J Pharm 2009;28:538-43

81. Darwish IAE, El-Kamel AH. Dissolution enhancement of glibenclamide using liquisolid tablet technology. Acta Pharm 2001;51:173-81

82. Liao CC, Jarowski CI. Dissolution rates of corticoid solutions dispersed on silicas. J Pharm Sci 1984;73:401-3

83. Hentzschel CM, Alnaief M, Smirnova I, et al. Hydrophilic silica aerogels and liquisolid systems – two drug delivery systems to enhance dissolution rates of poorly soluble drugs. 37th Annual Meeting & Exposition of the Controlled Release Society; Portland; 2010

Affiliation

Ali Nokhodchi[†1], Christina M Hentzschel[2] & Claudia S Leopold[2]
[†]Author for correspondence
[1]Universities of Kent and Greenwich, Medway School of Pharmacy, Chemistry and Drug Delivery Group, Chatham Maritime Kent, ME4 4TB, UK
Tel: +44 1634 202947;
E-mail: a.nokhodchi@kent.ac.uk
[2]University of Hamburg, Institute of Pharmacy, Department of Pharmaceutical Technology, Bundesstrasse 45, 20146 Hamburg, Germany