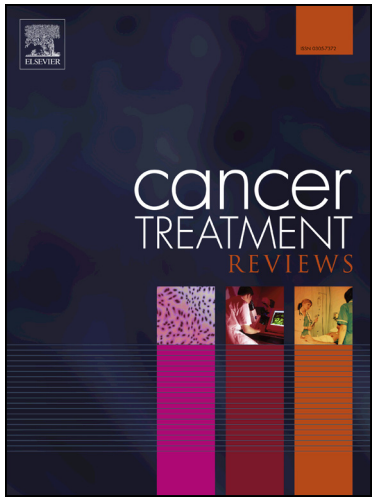

Inventory of oral anticancer agents: pharmaceutical formulation aspects with focus on the solid dispersion technique

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Inventory of oral anticancer agents: pharmaceutical formulation aspects with focus on the solid dispersion technique

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Inventory of oral anticancer agents: pharmaceutical formulation aspects with focus on the solid dispersion technique

Abstract

Dissolution from the pharmaceutical formulation is a prerequisite for complete and consistent absorption of any orally administered drug, including anticancer agents (oncolytics). Poor dissolution of an oncolytic can result in low oral bioavailability, high variability in blood concentrations and with that suboptimal or even failing therapy. This review discusses pharmaceutical formulation aspects and absorption pharmacokinetics of currently licensed orally administered oncolytics. In nearly half of orally dosed oncolytics poor dissolution is likely to play a major role in low and unpredictable absorption. Dissolution-limited drug absorption can be improved with a solid dispersion which is a formulation method that induces super-saturated drug dissolution and with that it enhances in-vivo absorption. This review discusses formulation principles with focus on the solid dispersion technology and how it works to enhance drug absorption. There are currently three licensed orally dosed oncolytics formulated as a solid dispersion (everolimus, vemurafenib and regorafenib) and these formulations result in remarkably improved dissolution and absorption compared to what can be achieved with conventional formulations of the respective oncolytics. Because of the successful implementation of these three solid dispersion formulations, we encourage the application of this formulation method for poorly soluble oral oncolytics.

Keywords: solid dispersion; solubility; dissolution; bioavailability; variability; pharmacokinetics

Abbreviations
ABC: ATP-binding cassette
BCS: Biopharmaceutics Classification System
BDDCS: Biopharmaceutics Drug Disposition Classification System
EPAR: European Public Assessment Report
FDA: Food and Drug Administration Agency
SEDDS: Self Emulsifying Drug Delivery System

1. Introduction

The treatment of cancer with chemotherapy is undergoing an “intravenous-to-oral” switch trend which has led to an increasing availability of oral formulations with anticancer drugs (oncolytics). The advantage is that oral formulations bypass the need for hospitalization to administer the drug, making it possible to treat cancer in a more home-based setting, which many cancer patients actually prefer [1–3]. Another advantage is that oral oncolytics make possible continuous chemotherapy schedules. An important group of oncolytics which are dosed continuously are the tyrosine kinase inhibitors which exert their antineoplastic action by interfering with tumor-specific molecular pathways, referred to as targeted chemotherapy [4]. A prerequisite for orally administered drugs, in particular for oncolytics, is a complete and consistent absorption process because these agents usually have a steep dose-response curve and a narrow therapeutic index [5]. In order to reach the systemic circulation the drug must dissolve from its pharmaceutical dosage form (capsule or tablet) in the gastro-intestinal fluid. The problem is that many drugs have a poor solubility in water which can lead to incomplete and unpredictable absorption and consequently in a negative treatment outcome such as under- or overdosing [4,6,7]. Moreover, absorption of low-solubility drugs can be significantly affected by food or drinks, e.g. by modifying the pH environment, which is obviously rather uncontrolled [8,9]. Therapeutic drug monitoring is one way to adjust the dose when inadequate in-vivo drug concentrations are achieved [5,10,11]. However, drugs with dissolution-limited absorption often result in high day-to-day variability in in-vivo drug concentrations (i.e. intra-patient variability) which is difficult to adjust to with therapeutic drug monitoring [11,12]. Besides, therapeutic drug monitoring adjusts doses retrospectively, requires extra healthcare infrastructure such as patient sampling and bioanalysis [10] and, what is more, it does not solve the problem of dissolution-limited absorption.

The core of the problem of dissolution-limited absorption might be addressed by optimization of the pharmaceutical formulation. Currently there are different formulation strategies at hand to enhance drug dissolution and a very promising one is the solid dispersion approach. There are currently 27 solid dispersion formulations commercially available (including 3 orally dosed oncolytics), with examples of achieving even a 30 times increased drug dissolution (i.e. vemurafenib solid dispersion), highlighting the feasibility and success of this formulation method [13,14].

This review discusses the basics of drug dissolution, focuses on the solid dispersion formulation technique and addresses which oral oncolytic formulations have dissolution-limited absorption pharmacokinetics and are potential candidates for a solid dispersion formulation.

2. Conventional pharmaceutical formulations and the basics of drug dissolution

As can be seen in Fig. 1, most of the commercially available oral oncolytics are physical mixture formulations (67%), followed by prodrugs (18%), lipid formulations (10%), solid dispersions (4%) and co-solvents (1%).

Physical mixtures contain mechanically mixed crystalline drug powder, filling powder (e.g. cellulose, lactose or starch), disintegrant (e.g. croscarmellose), glidant (e.g. silicon dioxide) and lubricant (e.g. magnesium stearate). To obtain the final dosage form, physical mixtures are pressed into tablets or filled in capsules. Physical mixtures are standard oral drug formulations because development of such a formulation is simple and inexpensive [15]. An example of a physical mixture formulation is anastrozole (Arimidex®). A schematic representation of what happens to a capsule or a tablet containing a physical powder mixture after oral intake is shown in Fig. 2. The shell of the capsule dissolves in water and the powder is then wetted. In the case of tablets, penetrating water breaks down the tablet into large particles (agglomerates) and then to finer particles [16,17]. The next step is solvation and is facilitated by water molecules surrounding the drug molecule. Solvated drug molecules then diffuse into the bulk environment volume, resulting in dissolution. Only dissolved drug molecules can pass epithelial cells in the gastro-intestinal tract for absorption [18].

A prodrug formulation contains a biologically inactive compound which is converted in-vivo to the pharmacologically active drug [19], a strategy which can be used if the active drug has poor oral absorption either due to poor dissolution or due to extensive metabolism. Prodrug powders are processed into a capsule or a tablet in the same way as physical mixtures. An example of a prodrug formulation in capecitabine (Xeloda®).

In lipid-based formulations the drug is dissolved or dispersed in lipid excipients (i.e. mono, di, or triglyceride). Endogenous lipid-digesting enzymes and bile-salts transform the lipid formulation into emulsification droplets, resulting in drug dissolution. Surfactants (i.e. polyglyceride fatty esters, polyethylene glycol) can be added to speed up the emulsification process and to enhance drug dissolution, a feature which is used in a self-emulsifying drug delivery system (SEDDS). SEDDS is an isotropic mixture of lipids, surfactants and co-solvents and when agitated in water it readily forms an emulsion with droplets < 300 nm. Lipid-based formulations can be liquid, solid or semi-solid. A disadvantage is that many lipid-based formulations require careful handling and storage because they can be physically and/or chemically unstable. Lipid-based formulations (in particular SEDDS) may contain high

amounts of surfactants (usually 30 – 60% of the formulation) and this can cause gastro-intestinal toxicity [20–23]. An example of a lipid-based formulation is tretinoin (Vesanoid®) and an example of a SEDDS is olaparib (Lynparza®).

A co-solvent formulation contains an organic solvent to increase drug dissolution in water (i.e. ethanol or propylene glycol). The disadvantage is that organic co-solvents can evaporate through capsule shells (even if the capsule is sealed) and this may lead to drug precipitation in the formulation. Besides organic solvents can be toxic [15,22]. An example of a co-solvent formulation is vinorelbine (Navelbine®).

Capsules or tablets may also have a coating: an extra layer on the exterior of the capsule or tablet. Coatings can be used to protect the dosage form against light, moisture and/or mechanical stress, to make the dosage form look more attractive/recognizable or for controlled disintegration. Regarding the latter, an example is an enteric-resistant coating which has a pH-dependent solubility (no solubility in stomach pH, high solubility in the intestine), hence the dosage form does not degrade in the stomach. This can be applied to drugs with poor stability in acidic pH such as in the stomach [24].

Factors affecting drug dissolution

The process of drug dissolution is influenced by parameters that are described in the Noyes-Whitney equation [25,26]:

$$\frac{dW}{dT} = D \times A \times \frac{Cs - C}{h}$$

Where dW/dt is drug dissolution rate during a certain period of time (e.g. mg/min), D the diffusion coefficient (e.g. cm^2/min), A the surface area of the drug (e.g. cm^2), C_s the saturation solubility of the drug (e.g. mg/L), C the concentration of the drug (e.g. mg/L) and h the thickness of the diffusion layer (e.g. cm). A is related to powder particle size (smaller particles result in a larger surface area), wettability of the powder and by surfactants in gastro-intestinal fluids and bile. D describes the diffusivity of a drug and is influenced by molecule size and viscosity of gastro-intestinal fluids. Parameter h is determined by the viscosity and surfactant concentration in gastro-intestinal fluids as well as by contractile patterns in the gastro-intestinal tract [4,18]. C_s is governed by intrinsic drug molecule properties such as molecular mass, Log P, the number of hydrogen donors/acceptors and the pK_a [18,27].

Biopharmaceutics Classification System (BCS) and Biopharmaceutics Drug Disposition Classification System (BDDCS)

There are two different systems that use biopharmaceutical properties of a drug molecule to predict drug absorption [28]. The biopharmaceutical classification system (BCS) classifies drugs by solubility in water and permeability across human epithelial cells. A drug can fall in either of the four classes: high solubility-high permeability (class I), low solubility-high permeability (class II), high solubility-low permeability (class III) and low solubility-low permeability (class IV) [28–30]. A drug is considered highly permeable if >90% of the dose is absorbed by epithelial cells and soluble when the highest dose strength dissolves in 250 mL water over pH range 1.2 – 7.4 [31].

The other system, BDDCS, describes the biopharmaceutics of a drug by solubility in water and in-vivo disposition. Criteria for solubility in water are the same as used with BCS. The disposition of a drug is influenced by enzymatic, - and transporter processes, consequently BDDCS describes whether a drug undergoes first-pass metabolism and whether it is a substrate to drug efflux transporters such as ATP-binding cassette transporters (ABC) [4,32,33]. Drugs with high permeability are readily absorbed, facilitating access to metabolic enzymes and this then results in high metabolism. This makes BDDCS more representative to describe the absorption pharmacokinetics of a drug [28,30]. BDDCS classes are: high solubility-high metabolism (class I), low solubility-high metabolism (class II), high solubility-low metabolism (class III) and low solubility-low metabolism (class IV).

Currently, 90% of orally administered drugs in clinical development are categorized as BCS/BDDCS II or IV [30] and 40% fails because of insufficient biopharmaceutical properties such as poor drug dissolution [18]. This underlines that the pharmaceutical formulation is a crucial part in drug development.

3. Solid dispersions

A solid dispersion consists of a drug that is dispersed in a hydrophilic excipient which can be a small molecule such as urea or sugar [34] or a biologically inactive polymer such as cellulose derivatives, polyethyleneglycols, polyvinylpyrrolidones, polyvinylalcohols, polyacrylates and sugar polyols [35–37]. A solid dispersion is not just a physical powder mixture of drug and excipient. Instead, a solid dispersion consists of powder particles in

which drug and excipient are integrated and therefore appears as a one-phase powder, with considerably smaller powder particles than what can be achieved with mechanical milling processes [6,7,33,35,38–42]. The very fine dispersion of drug and excipient, decreased particle size and the hydrophilic character of the excipient result in enhanced drug dissolution [43].

Types of solid dispersions

An important feature of a solid dispersion is the physical state of the powder: it can be crystalline or amorphous [37,40,44]. The difference between crystalline powders and amorphous powders is illustrated in Table 1. Crystalline powders contain molecules that are arranged in a highly ordered way. The lattice structure in a crystal results in rigid and physically stable powder particles. Crystalline particles are relatively large and coarse (usually 50 - 1000 µm [45]). Water must first break down the lattice energy holding the crystal together in order to allow solvation and then drug dissolution. Amorphous powders are irregularly organized molecules with considerably smaller particle size, usually < 50 µm. Consequently, the particle surface area of amorphous powders is larger than that of crystalline powders. The absence of lattice energy bonds and the larger particle surface area of amorphous powders result in higher drug dissolution [46]. The disadvantage of amorphous powders, however, is that the molecular structure is physically unstable and over time crystal bonding between molecules develops, affecting the dissolution [43,46]. This makes it difficult to retain an amorphous powder. Table 1 also compares drug dissolution from a crystalline powder and an amorphous powder: the saturation solubility from an amorphous powder is higher than from a crystalline powder and is then “super-saturated”. The highest concentration in this phase is known as S_{max}. The super-saturated state is temporarily because the drug precipitates back to the saturation concentration equal to that of the crystal form, $S_{equilibrium}$. The moment that precipitation starts, is the precipitation onset time, $T_{precipitation}$. The temporarily super-saturated drug solution creates a time window for enhanced in-vivo absorption. The role of the hydrophilic excipient in a solid dispersion is to support super-saturation and to inhibit precipitation [14,40,43].

The type of the solid dispersion is determined by the physical state of drug and excipient (crystalline or amorphous). There are crystalline solid dispersions, amorphous solid dispersions and crystalline-amorphous solid dispersions and their characteristics are shown in Table 2.

First, among crystalline solid dispersions are the *eutectic mixtures* which were actually the first known solid dispersions [40]. Eutectic solid dispersions are made by heating up a powder mixture at weight proportions at which drug and excipient melt simultaneously,

followed by a cooling-down phase [34,40]. Each compound has its own specific melting temperature but when used in a particular weight proportion the mixture can melt simultaneously [40] and the temperature at which this occurs is called the eutectic temperature [34]. Because the eutectic temperature is lower than the melting temperature of the individual compounds of the mixture, the production temperature can be reduced which is particularly advantageous for thermally unstable compounds. The advantage of an eutectic mixture is that drug and excipient are more homogenously mixed than in physical mixtures and this results in higher drug dissolution [37,40].

Another type of crystalline solid dispersions are *solid solutions* [34]. In solid solutions a crystalline drug is "dissolved" in a crystalline excipient which results in a single-phase powder because the lattice of the crystal consists of excipient molecules and of drug molecules. Solid solutions have smaller particles than pure crystalline drug compounds and are more homogenous than physical mixtures. This contributes to higher dissolution and absorption [40]. For example, griseofulvin-polyethylene glycol 4000 solid solution resulted in a ~2 times higher in-vivo exposure compared to crystalline griseofulvin [40].

In an *amorphous solid dispersion* (i.e. *glass solution*) the drug "dissolves" in an amorphous excipient resulting in a one-phase amorphous powder [34,40,47]. The amorphous state of the powder, homogeneously mixed at molecular level, the hydrophilic character of the excipient and the large surface area result in high dissolution and absorption enhancement [40]. For example, the antiviral drug telaprevir (Incivo®) is an amorphous solid dispersion with ~32 times increased dissolution and ~10 increased bioavailability [48]. The disadvantage of amorphous solid dispersions is that they can be unstable because amorphous materials can revert to crystalline forms [34]. Therefore, amorphous solid dispersions require more careful handling and storage than crystalline solid dispersions [47].

In a *glass suspension* an amorphous drug is not entirely dissolved in an amorphous excipient [40,47]. Instead the drug is dispersed as amorphous clusters or is partially amorphous-partially crystalline [40]. Glass suspensions may occur when the amount of drug in the solid dispersion is relatively large (usually at ≥ 35%). Drug recrystallization is more likely to occur during storage and this makes glass suspensions less stable than glass solutions [47].

In *amorphous precipitates* the drug precipitates out as an amorphous form and is dispersed in a crystalline excipient [40,44]. The amorphous form of the drug and the hydrophilic character of the excipient contribute towards dissolution enhancement. For example, an amorphous dispersion of ritonavir in crystalline polyethyleneglycol 8000 resulted in a 3.5 - 5 times increased dissolution and a 11 - 22 times improved absorption compared to a crystalline physical mixture of ritonavir-polyethylene glycol 8000 [49,50].

Production methods

There are four production methods for solid dispersions: solvent-removing, melting, precipitation and electro-spinning [34,35,37,41,44,51–53]. In the solvent-removal method, drug and excipient are dissolved in an organic solvent and the solution is then evaporated or sublimated. A commonly used evaporation apparatus is a spray dryer and works by transforming the solution into droplets which are dried with a gas (i.e. nitrogen or air) [52]. A common sublimation apparatus is a freeze dryer which freezes the solution and then induces solvent removal by reducing the air pressure [47].

In the melting method drug and excipient are mixed and then heated until they melt. The melt mixture is then rapidly cooled and this ensures that drug and excipient stay molecularly mixed. The result is a solid mass which is then pulverized to obtain particles of a desired size [37,44]. A commonly used apparatus is a hot melt extruder [54].

In the precipitation process drug and excipient are dissolved in a solvent and then an anti-solvent is added to induce precipitation. This results in a precipitate which is further dried to remove residual solvents and finally a dry powder is obtained [13].

In electro-spinning a solution of drug and excipient is dried with electrical energy. The solution is placed in a syringe with a metal tip and pressed out with a pump. The application of high voltage between the metal tip of the syringe and metallic collecting material ejects elongated droplets from the syringe which then evaporate and the resulting product is a solid fiber [55].

Examples of commercialized solid dispersion formulations

In the field of oncology there are currently three commercialized formulations that contain a solid dispersion: vemurafenib, regorafenib and everolimus. Information sources for this paragraph are the European Public Assessment Report (EPAR), U.S. Food and Drug Administration (FDA) drug approval package and literature.

Vemurafenib (Zelboraf®, Roche)

Vemurafenib formulation was initially a physical mixture of crystalline vemurafenib in a capsule. However, the physical mixture resulted in poor bioavailability and a formulation switch to the solid dispersion technique was performed during clinical evaluation [13]. Zelboraf® is an amorphous solid dispersion of vemurafenib-hypromellose acetate succinate (30:70, m/m). The solid dispersion is prepared through precipitation in which vemurafenib and hypromellose acetate succinate are dissolved in the solvent dimethylacetamide and then the anti-solvent dilute hydrochloric acid (0.01 N) induces precipitation of vemurafenib and hypromellose acetate succinate [13]. The precipitate is vacuum-dried, compressed into

tablets and film-coated. Vemurafenib dissolution from the solid dispersion is ~30 times higher than that of crystalline vemurafenib and results in approximately 5 times higher vemurafenib plasma concentrations [13] (see also Fig. 3).

Regorafenib (Stivarga®, Bayer)

Regorafenib is practically insoluble in water and therefore a tablet was developed containing an amorphous solid dispersion of regorafenib-povidone K25. Regorafenib dissolution from the amorphous solid dispersion is ~4.5 times higher than from a physical mixture of regorafenib-povidone K25 [56] and the bioavailability is ~7 times higher than that of a crystalline tablet formulation.

Everolimus (Afinitor®, Votubia®, Certican®, Novartis)

Everolimus is practically insoluble in water and therefore a tablet containing a spray dried amorphous solid dispersion formulation of everolimus-hydroxypropyl methylcellulose (1:40, m/m) has been developed. The formulation also contains butylhydroxytoluene to prevent oxidation of everolimus. The dissolution from the solid dispersion is approximately 4 times higher than from crystalline powder [57]. Certican® was the first licensed formulation for prophylaxis of transplanted organ rejections and was developed in tablet strengths 0.25 mg, 0.5 mg, 0.75 mg and 1 mg. Thereafter, the oncology tablet, Afinitor®, was developed in tablet strengths 2.5 mg, 5 mg and 10 mg, the qualitative composition and drug-excipient proportions being equivalent to Certican®. Votubia® 2.5 mg, 5 mg and 10 mg tablets contain the same formulation as Afinitor® tablets but is licensed as an orphan drug for tuberous sclerosis.

4. Biopharmaceutics and absorption pharmacokinetics of oral oncolytics

The absorption pharmacokinetics of commercially available oral oncolytics are shown in Table 3. Dissolution-limited absorption is defined by the BCS/BDDCS status of the drug, incomplete oral bioavailability and high variability in concentrations/exposure in blood (whole blood, plasma or serum) by criteria:

1. The drug is classified as BCS/BDDCS II or IV;
2. Oral bioavailability < 85% [28];
3. Intra-patient variability in exposure ≥ 30% [12].

In the case of unknown bioavailability and/or unknown intra-patient variability, a lack of a linear relationship between dose and concentration/exposure in blood and inter-patient

variability ≥ 70% are criteria for dissolution-limited absorption. The cut-off value for inter-patient variability is based on the fact that the upper limit of the 95% confidence interval of BCS/BDDCS I/III drugs studied in this review (Table 3) is 67%.

Of the 72 studied oral oncolytics 47 are BCS/BDDCS II or IV drugs which means that 65% of oral oncolytics are poorly soluble in water. 34 out of 72 (47%) oncolytics are inadequately absorbed from the gastro-intestinal tract as a result of a poor dissolution from the pharmaceutical formulation, manifested as low bioavailability, high variability in blood concentrations and lack of a linear relationship between dose and blood concentrations. Because many oncolytics are highly potent with a steep dose-response curve, incomplete and highly variable absorption might result in treatment failure or toxicity. Improving the formulation of oral oncolytics with dissolution-limited absorption seems considerable and the solid dispersion could then be a technique of interest. Currently, only three oncolytics are commercially available as solid dispersion formulations (vemurafenib, regorafenib and everolimus) but demonstrate that drug absorption can be significantly improved, highlighting the feasibility and success of this formulation method. Therefore, we encourage research, development and widespread application of the solid dispersion technique for oral oncolytics.

5. Conclusions

A crucial characteristic for complete and predictable absorption of an orally administered oncolytic is that the drug dissolves in gastro-intestinal fluids. The problem is that many orally administered oncolytics are poorly soluble in water. In half of the currently licensed arsenal of oral oncolytics poor drug dissolution is likely to play a major role in poor absorption pharmacokinetics such as incomplete bioavailability, high intra-patient variability in blood concentrations and lack of linear relationship between dose and blood concentrations. Dissolution-limited absorption might be resolved with the solid dispersion technology because this formulation method can induce super-saturated drug dissolution and with that enhanced absorption. There are three licensed oral oncolytics with a solid dispersion formulation: vemurafenib, regorafenib and everolimus and they result in a significantly increased dissolution and enhanced absorption relative to their corresponding crystalline physical mixture formulations. We believe that the solid dispersion can be feasible and successful for improving dissolution-limited absorption of poorly soluble drugs and encourage the application of this formulation method in the pharmaceutical development of oral oncolytics.

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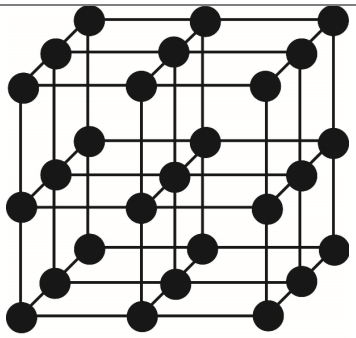
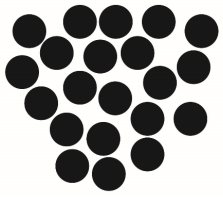
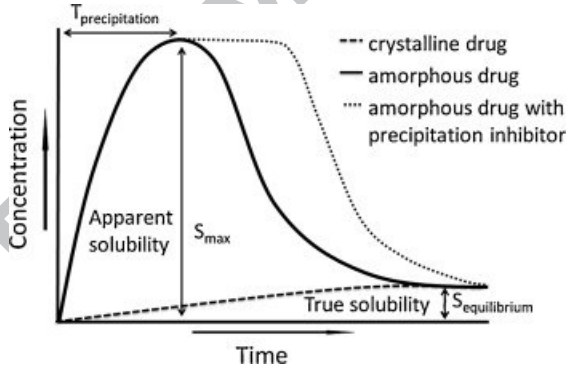
Tables

Table 1 Pharmaceutical features of a crystalline powder drug particle and an amorphous drug powder particle

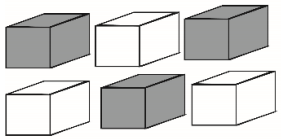
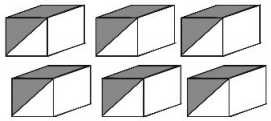
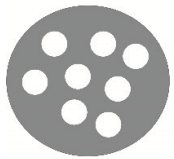
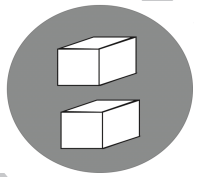
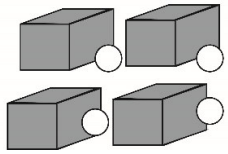
Feature	Crystalline	Amorphous
Schematic structure of one powder particle	 ● = one drug molecule, — = crystal bond	
Molecule orientation	Regular	Irregular
Particle size	Large	Small
Particle surface area	Small	Large
Stability physical structure	Strong	Weak
Dissolution	 Reprinted from Moes et al [58] with permission from Elsevier. Precipitation inhibitor is the hydrophilic excipient of a solid dispersion which supports super-saturation and increases $T_{preciptitation}$.	

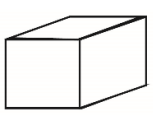
S_{max}: highest apparent solubility

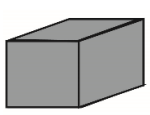
$T_{precipitation}$: time at which drug starts to precipitate after having reached its highest apparent solubility

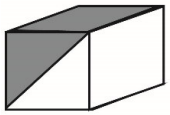
$S_{equilibrium}$: intrinsic solubility of the drug

Table 2 Type of solid dispersions and their pharmaceutical features, classification based on [34,37,40,44].

	CRYSTALLINE SOLID DISPERSIONS		**AMORPHOUS SOLID DISPERSIONS**	**AMORPHOUS-CRYSTALLINE SOLID DISPERSIONS**	
	Eutectic mixture	**Solid solution**	**Glass solution**	**Glass suspension**	**Amorphous precipitate**
Number of phases	2	1	1	2	2
Drug	Crystalline	Crystalline	Amorphous	Crystalline	Amorphous
Hydrophilic excipient	Crystalline	Crystalline	Amorphous	Amorphous	Crystalline
Schematic picture					


Drug crystal


excipient crystal


drug/excipient crystal


amorphous excipient

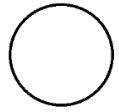

amorphous drug

Table 3 Biopharmaceutical properties and absorption pharmacokinetics of licensed oral oncolytics in Europe on 04-09-2016 (searched EudraPharm database www.eudrapharm.eu and CBG Medicine Information Bank www.cbg-meb.nl by ATC-code "L01" and administration route "oral"). Grey-shaded rows indicate drug formulations with solubility-limited absorption. L = linear, NL = not linear. QD = once daily, BID = twice daily, TID = thrice daily, QW = once a week. Q2D = once every second day, NA = not available. EPAR = European Public Assessment Report, www.ema.europa.eu. FDA = U.S. Food and Drug Administration drug approval package, www.accessdata.fda.gov/scripts/cder/drugsatfda

Drug substance	Drug product	Formulation and amount of active drug	Solubility in water (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Abiraterone acetate	Zytiga®	Prodrug- Physical mixture Tablet 250 mg	0.11 (pH 1) 0.02 (pH 2) < 0.01 (pH 5)	IV	≤ 10	IaP: 71 % IerP: 33 – 141 %	250 – 1000 mg QD: L	1000 mg QD	Fasted	[59], FDA, EPAR
Afatinib dimaleate	Giotrif®	Physical mixture Tablet 20, 30, 40, 50 mg	50 (pH < 6)	I or III	NA	IaP: 33 % IerP: 57 – 105 %	10 – 100 mg: NL	40 mg QD	Fasted	FDA, EPAR
5-Amino levulinic acid hydrochloride	Gliolan®	Crystalline powder for oral solution 30 mg/mL	100 – 1000	I	100	IaP: NA IerP: 4 – 13%	0.2 – 20 mg/kg: L	20 mg/kg before surgery	Fasted	EPAR
Anagrelide hydrochloride	Xagrid® Agrylin®	Physical mixture Capsule 0.5 mg	0.1 – 1	I or III	≥ 70	NA	0.5 – 2 mg: L	0.5 – 2.5 mg BID	Fasted or fed	[60], FDA, EPAR
Anastrozole	Arimidex®	Physical mixture Tablet 1 mg	0.5	III	NA	NA	0.1 – 60 mg: L	1 mg QD 5 years	Fasted or fed	[39,61,62], FDA
Axitinib	Inlyta®	Physical mixture Tablet 1, 3, 5, 7 mg	1.8 (pH 1) 0.3 (pH 1.7) 0.01 (pH 3) 0.0002 (pH 5 – 7.8)	II	58	IaP: 20 - 22% IerP: 80 %	1 – 20 mg BID: L	5 mg BID	Fasted or fed	FDA, EPAR
Bexarotene	Targretin®	Lipid-based Capsule 75 mg	< 0.1	II	NA	IaP: 25 – 105 % IerP: 11 – 83 %	21 – 800 mg/m^2 QD: L	300 mg/m^2 QD	Fed	[39,63–65], EPAR
Bicalutamide	Casodex®	Physical mixture Tablet 50 mg, 150 mg	0.005	II	NA	NA	10 – 30 mg QD: L 30 – 200 mg QD: NL	50 – 150 mg QD	Fasted or fed	[30,66], FDA

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure or blood / plasma concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose proportionality	Recommended dose	Fed or fasted	Reference
Bosutinib monohydrate	Bosulif®	Physical mixture Tablet 100 mg, 500 mg	11.0 (pH 1) 2.7 (pH 5.0) 0.02 (pH 6.8)	IV	34	IaP: 19 – 31 % IerP: 58 – 73 %	300 – 600 mg QD: NL	500 - 600 mg QD	Fed	[67], FDA, EPAR
Busulfan	Myleran®	Physical mixture Tablet 2 mg	0.1	II	68 - 80	IaP: 31% IerP: 24 - 46 %	NA	0.5 – 8 mg per day or 1 mg/kg 4 times a day for 4 days	NA	[30,68–75], FDA
Cabozantinib S-maleate	Cometriq®	Physical mixture Capsule 20, 80 mg	< 0.1 (pH > 4)	II	NA	IaP: 25 – 34 % IerP: 37 – 61 %	100 – 175 mg QD: L 175 – 250 mg QD: NL	140 mg QD	Fasted	FDA, EPAR
Capecitabine	Xeloda®	Prodrug-Physical mixture Tablet 150, 500 mg	26	I	~100	IaP: NA IerP: 27 – 89%	251 - 1757 mg/m^2/day in 2 doses: L	800 - 1250 mg/m^2 BID 14 days or 625 mg/m^2 BID continuously	Fed	[30,76–78], EPAR, FDA
Ceritinib	Zykadia®	Physical mixture Capsule 150 mg	12 (pH 1) 0.03 (pH 4.5) 0.01 (pH 6.8)	IV	NA	IaP: NA IerP: 74 – 93 %	50 – 750 mg: L	750 mg QD	Fasted	FDA, EPAR
Chlorambucil	Leukeran®	Physical mixture Tablet 2 mg	< 0.1	NA	> 70	IaP: NA IerP: 36 – 84%	15 – 70 mg single dose: L	4 – 15 mg QD 3 – 8 weeks	NA	[79–82], FDA
Cobimetinib hemifumarate	Cotellic®	Physical mixture Tablet 20 mg	48 (pH 2) 1.1 (pH 4.5) 0.8 (pH 6.8 - 7.5)	I	46	IaP: NA IerP: 60 %	10 – 100 mg QD: L	60 mg QD 21 days	Fasted or fed	FDA, EPAR
Crizotinib	Xalkori®	Physical mixture Capsule 200, 250 mg	0.034	IV	43	IaP: NA IerP: 28 – 44 %	50 – 300 mg single dose: NL	250 mg BID	Fasted or fed	[83], FDA, EPAR

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure/ concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose-proportionality	Recommended dose	Fed or fasted	Reference
Cyclophosphamide monohydrate	Cytoxan® Endoxan®	Physical mixture Tablet 50 mg	40	I	> 85	NA	NA	1 – 5 mg/kg QD	Fasted or fed	[30,84], FDA
Dabrafenib mesylate	Tafinlar®	Physical mixture Capsule 50, 75 mg	1 – 0.1 (pH 1) < 0.1 (pH > 4) 0.007 (pH 6)	II	95%	IaP: NA IerP: 37 – 38 %	12 mg – 300 mg BID: NL	150 mg BID	Fasted	FDA, EPAR
Dasatinib monohydrate	Sprycel®	Physical mixture Tablet 20, 50, 70, 80, 100, 140 mg	18 (pH 2.6) 0.205 (pH 4.28) 0.008 (pH 6.0)	II	NA	IaP: 44 % IerP: 33 %	15 – 180 mg QD: L	100 – 140 mg QD	Fasted or fed	[85], FDA, EPAR
Enzalutamide	Xtandi®	Lipid-based Capsule 40 mg	0.002 (pH 1 – 7)	II	≥ 84	IaP: 59% IerP: 19 – 80 %	30 – 360 mg QD: L	160 mg QD	Fasted or fed	FDA, EPAR
Erlotinib hydrochloride	Tarceva®	Physical mixture Tablet 25, 100, 150 mg	0.4 (pH 2) < 0.4 (pH > 2)	II	59	IaP: 16 – 38 % IerP: 60%	100 – 1000 mg single dose: NL	100 - 150 mg QD	Fasted	[86,87], FDA, EPAR
Estramustine phosphate disodium	Estracyt® Emcyt®	Prodrug-Physical mixture Capsule 140 mg	100 - 1000	I or III	44	IaP: NA IerP: 21 %	70 – 560 mg/day: L	10 – 16 mg/kg per day in 2 – 4 divided doses	Fasted, not with dairy products	[82,88,89], FDA
Etoposide	Vepesid®	Lipid-based Capsules 50 mg, 100 mg	< 0.1	IV	65	IaP: 23 % IerP: 35 - 58%	25 – 200 mg: L > 300 mg: NL	100 – 200 mg/m^2 QD or 200 mg/m^2 Q2D during 5 days	Fasted	[39,82,90, 91], FDA
Everolimus	Afinitor® Votubia® Certican®	Solid dispersion Tablet 0.25, 0.5, 0.75, 1, 2.5, 5, 10 mg Dispersible tablet 2, 3, 5 mg	0.0096	IV	NA	IaP: 17 – 19 % IerP: 36 – 51 %	5 – 20 mg: L	10 mg QD	Fasted or fed	[92], FDA, EPAR

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure/ concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose-proportionality	Recommended dose	Fed or fasted	Reference
Exemestane	Aromasin®	Physical mixture Tablet 25 mg	0.086 (pH 1.5) 0.079 (pH 5.5) 0.073 (pH 7.4)	II	NA	IaP: NA IerP: 39 – 100 %	25 – 200 mg single dose: L	25 mg QD	Fed	[30], FDA
Fludarabine mono phosphate	Fludara®	Prodrug-Physical mixture Tablet 10 mg	1 – 10	I	~ 55	IaP: NA IerP: 32 – 56 %	50 – 90 mg/day single dose: L	40 mg/m^2 QD 5 days	Fasted or fed	[30,82,93, 94], FDA
Gefitinib	Iressa®	Physical mixture Tablet 250 mg	1 (pH 1 - 4) 0.4 (pH 5) 0.01 (pH 6) < 0.01 (pH ≥ 6.8)	II	59%	IaP: 4 – 42 % IerP: 27 – 65 %	50 – 250 mg QD: L > 250 mg QD: NL	250 mg QD	Fed or fasted	[86,95], FDA, EPAR
Gimeracil	Teysuno®	Physical mixture Capsule 4.35, 5.8 mg	1 – 10	III	≥ 44	IaP: NA IerP: 12 – 33%	25 – 40 mg/m^2: L	10 mg/m^2 BID 21 days	Fasted	[96], EPAR
Hydroxycarbamide	Siklos® Hydrea®	Physical mixture Tablet 100, 1000 mg Capsule 500 mg	100 – 1000	I	~100	NA	NA	15 – 30 mg/kg QD	Fasted or lightly-fed	EPAR
Ibrutinib	Imbruvica®	Physical mixture Capsule 140 mg	2 (pH 1.2) 0.06 (pH 3) 0.003 (pH 4.5 – 8)	II	3 - 6	IaP: 27 – 43% IerP: 41 – 136%	420 – 840 mg: L	420 – 560 mg QD	Fasted or fed	FDA, EPAR
Idarubicin hydrochloride	Zavedos®	Physical mixture Capsule 5, 10, 25 mg	1	I	41	IaP: 25 % IerP: 33%	NA	15 - 30 mg/m^2 QD 3 days or 30 – 50 mg/m^2 single dose per 3 weeks	NA	[30,97,98]
Idelalisib	Zydelig®	Physical mixture Tablet 100, 150 mg	1.1 (pH 1.2) < 0.10 (pH 7.7)	II	NA	IaP: 53% IerP: NA	50 – 350 mg BID: NL	150 mg BID	Fasted or fed	FDA, EPAR

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure/ concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose-proportionality	Recommended dose	Fed or fasted	Reference
Imatinib mesylate	Glivec® Gleevec®	Physical mixture Capsule 50 mg, 100 mg Tablet 100 mg, 400 mg	33 - 100 (pH < 5.5) 0.050 (pH 7.4)	II	98	IaP: 64 % IerP: 31 – 66 %	25 – 1000 mg QD: L	100 – 600 mg QD, 400 mg BID	Fed	[99,100], FDA, EPAR
Lapatinib ditysolate	Tykerb® Tyverb®	Physical mixture Tablet 250 mg	0.007 (water) 0.001 (pH 1)	IV	< 25	IaP: 30 – 36% IerP: 45 – 99 %	500 – 1600 mg QD: NL	1000 - 1500 mg QD	Fasted	[86], FDA, EPAR
Lenalidomide	Revlimid®	Physical mixture Capsule 2.5, 5. 7.5, 10, 15, 20, 25 mg	18 (pH 1) 0.4 – 0.5 (pH > 1)	III	≥ 85	IaP: 9 – 18 % IerP: 14 – 63 %	5 – 400 mg QD: L	10 - 25 mg QD 21 days	Fasted or fed	FDA, EPAR
Lenvatinib mesilate	Levima®	Physical mixture Capsule 4, 10 mg	< 0.1 (pH 3 – 7)	II or IV	NA	IaP: NA IerP: 19 – 78%	3.2 – 32 mg QD: L	18 - 24 mg QD	Fasted or fed	[101], FDA, EPAR
Letrozole	Femara®	Physical mixture Tablet 2.5 mg	0.04	I	100	IaP: NA IerP: 30 – 60 %	0.01 – 10 mg single dose: L	2.5 mg QD	Fasted or fed	[30], FDA
Lomustine	Belustine®	Prodrug-Physical mixture Capsules 40 mg	< 0.05	II or IV	≥ 73	IaP: NA IerP: 51 – 62 %	NA	100 - 130 mg/m^2 single dose per 6 weeks	Fasted	[102–104], FDA
Melphalan	Alkeran®	Physical mixture Tablet 2 mg	< 0.1	II or IV	56 – 93	IaP: NA IerP: 47%	NA	6 – 10 mg QD 4-10days, 2 mg QD	NA	[105,106], FDA
Mercaptopurine monohydrate	Puri-Nethol® Xalupurine®	Prodrug-Physical mixture Suspension 20 mg/mL Tablet 50 mg	< 0.1	II	5 – 37	IaP: 45% IerP: tabet 39 - 69% Suspension 30 - 46%	20 – 100 mg/m^2 QD: NL	25 – 75 mg/m^2 QD	Fasted, not with dairy products	[30,107–109], FDA, EPAR
Drug substance	**Drug product**	**Formulation and amount of active drug**	**Solubility (mg/mL)**	**BCS/ BDDCS**	**F (%)**	**Variability in-vivo exposure/**	**Dose-proportionality**	**Recommended dose**	**Fed or fasted**	**Reference**

						concentrations **Intra-patient (IaP)** **Inter-patient (IerP)**				
Methotrexate disodium	Methotrexate	Prodrug-Physical mixture Tablet 2.5, 7.5, 10 mg	< 0.1	II or IV	18 - 42	IaP: 20% IerP: NA	13 – 76 mg/m^2: NL	15 – 40 mg/m^2 QW or 10 – 30 mg QD 4 - 8 days	Fasted, not with dairy products	[82,110–113], FDA
Mitotane	Lysodren®	Physical mixture Tablet 500 mg	< 0.1	II or IV	35 - 40	NA	NA	2 – 6 g QD in 3-4 doses	Fed, high-fat meal	FDA, EPAR
Nilotinib hydrochloride monohydrate	Tasigna®	Physical mixture Capsule 150, 200 mg	1 – 10 (pH 1) 0.1 – 1 (pH 2 – 3) < 0.1 (pH ≥ 4.5)	IV	NA	IaP: 31 - 44 % IerP: 30 – 70 %	400 – 600 mg BID: NL	300 - 400 mg BID	Fasted	FDA, EPAR
Nintedanib ethanesulfonate	Ofev® Vergatef®	Lipid-based Capsule 100, 150 mg	5.0 (pH ≤ 4.5) 4.3 (pH 5) < 0.1 (pH ≥ 6.0)	II or IV	5	IaP: 33% IerP: 42 %	150 – 300 mg BID: L	200 mg BID 20 days	Fed	FDA, EPAR
Olaparib	Lynparza®	Lipid-based Capsule 50 mg	0.1 (pH 1 – 6.8)	IV	NA	IaP: NA IerP: 65 – 74%	100 – 600 mg BID: NL	400 mg BID	Fasted	FDA, EPAR
Osimertinib mesylate	Tagrisso®	Physical mixture Tablet 40, 80 mg	1 – 10 (pH 1.2) 10 – 33 (pH 4.6) 0.6 (pH 7) 0.07 (pH 7.5)	III	> 80	IaP: NA IerP: 40 – 50 %	20 – 240 mg QD: L	80 mg QD	Fasted or fed	FDA, EPAR
Oteracil mono-potassium	Teysuno®	Physical mixture Capsule 11.8, 15.8 mg	1 – 10 (pH 2 – 8)	III	≥ 13	IaP: NA IerP: 38 – 62 %	25 – 40 mg/m^2: L	25 mg/m^2 BID 21 days	Fasted	[96], EPAR
Panobinostat lactate	Farydak®	Physical mixture Capsule 10, 15, 20 mg	1.1 (pH 1 – 2) 4.8 (pH 4.5) 0.3 (pH 6.8) 0.06 (pH 7.6)	II	21	IaP: 38 – 52% IerP: 66 – 80 %	10 – 80 mg Q2D: NL	20 mg Q2D for 2 weeks	Fasted or fed	FDA, EPAR
Pazopanib hydrochloride	Votrient®	Physical mixture Tablet 200, 400 mg	1 – 10 (pH 1) < 0.1 (pH ≥ 4)	II	14 – 39	IaP: 26% IerP: 40 %	50 – 2000 mg QD: NL	800 mg QD	Fasted	[114], FDA, EPAR

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure/ concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose-proportionality	Recommended dose	Fed or fasted	Reference
Pomalidomide	Imnovid® Pomalyst®	Physical mixture Capsule 1, 2, 3, 4 mg	0.014 (pH 1.2 – 6.8)	IV	NA	IaP: 11 – 46 % IerP: 21 – 55 %	1 – 50 mg QD: NL	4 mg QD 21 days	Fasted or fed	FDA, EPAR
Ponatinib hydrochloride	Iclusig®	Physical mixture Tablet 15, 30, 45 mg	7.8 (pH 1.7) 0.0034 (pH 2.7) 0.00016 (pH 7.5)	II or IV	NA	IaP: NA IerP: 70%	15 – 60 mg: NL	45 mg QD	Fasted or fed	FDA, EPAR
Procarbazine hydrochloride	Natulan® Matulane®	Prodrug-Physical mixture Capsule 50 mg	100 – 1000	NA	≥ 70	IaP: NA IerP: 38 – 106%	NA	100 – 200 mg/m^2 per day	NA	[115–117]
Regorafenib monohydrate	Stivarga®	Solid dispersion Tablet 40 mg	0.0026 (pH 4.5 + 0.1% sodium dodecyl sulphate) < 0.1 (water)	II	NA	IaP: 32 – 64 % IerP: 43 – 182 %	60 – 160 mg single dose: L > 60 mg QD: NL	160 mg QD 21 days	Fed, low-fat meal	[56], FDA, EPAR
Ruxolitinib phosphate	Jakavi®	Physical mixture Tablet 5, 10, 15, 20 mg	> 0.5 (pH ≤ 3.3) 0.15 (pH 7.5)	I	96	IaP: NA IerP: 2 – 57%	10 – 50 mg BID: L	5 – 25 mg BID	Fasted or fed	FDA, EPAR
Sonidegib diphosphate	Odomzo®	Physical mixture Capsule 200 mg	< 0.0002 (pH > 2)	II	~5	IaP: NA IerP: 60 – 65 %	100 – 200 mg QD: L ≥ 200 mg QD: NL	200 mg QD	Fasted	FDA, EPAR
Sorafenib tosylate	Nexavar®	Physical mixture Tablet 200 mg	0.00034 (pH 1) 0.00013 (pH 4.5)	II	NA	IaP: 44 – 47% IerP: 36 – 91%	200 – 400 mg BID: L > 400 mg BID: NL	400 mg BID	Fasted or fed (low or moderate-fat meal)	FDA, EPAR
Sunitinib maleate	Sutent®	Physical mixture Capsule 12.5, 25, 37.5, 50 mg	25 (pH 1.2 – 6.8) < 0.1 (pH > 6.8)	IV	NA	IaP: 29 – 52 % IerP: 25 – 60 %	25 – 100 mg QD: L	50 mg QD 28 days or 37.5 mg QD	Fasted or fed	FDA, EPAR

Drug substance	Drug product	Formulation and amount of active drug	Solubility (mg/mL)	BCS/ BDDCS	F (%)	Variability in-vivo exposure/ concentrations Intra-patient (IaP) Inter-patient (IerP)	Dose-proportionality	Recommended dose	Fed or fasted	Reference
Tamoxifen citrate	Tamoxifen®	Prodrug-Physical mixture Tablet 10, 20, 30, 40 mg	0.5 (water) 0.2 (pH 1.7)	II	100	IaP: 12 – 15 % IerP: 51 – 69 %	NA	20 mg QD – 20 mg BID	Fasted or fed	[39,118,119], FDA
Tegafur	Teysuno®	Prodrug-Physical mixture Capsule 15, 20 mg	NA	I	> 83	IaP: NA IerP: 45 %	25 – 50 mg/m^2 QD: L	25 mg/m^2 BID 21 days	Fasted	[96], EPAR
Temozolomide	Temodal® Temodar® Temomedac®	Prodrug-Physical mixture Capsule 5, 20, 100, 140, 180, 250 mg	2 – 4 (water)	I or II	100	IaP: NA IerP: 4 – 56 %	100 – 250 mg/m^2 QD: L	75 mg/m^2 QD 42 days, 150 – 200 mg/m^2 QD 5 days	Fasted	FDA, EPAR
Thalidomide	Synovir®	Physical mixture Capsule 50 mg	0.05	II or IV	NA	IaP: NA IerP: 17 – 53%	50 – 400 mg single dose: NL	100 – 400 mg QHS 42 days	Fasted or fed	[30], FDA, EPAR
Thioguanine	Tabloid® Lanvis®	Prodrug-Physical mixture Tablet 40 mg	< 0.1	II or IV	14 – 46	Iap: NA IerP: 83 %	NA	60 - 200 mg/m^2 QD	NA	[116,120], FDA
Tipiracil hydrochloride	Lonsurf®	Physical mixture Tablet 6.14, 8.19 mg	120 (pH 1.2 – 7.5)	III	< 50	IaP: 29 – 36% IerP: 54 – 59 %	6.14 – 14.3 mg/m^2: L	14.3 mg/m^2 BID 5 days	Fed	FDA, EPAR
Topotecan hydrochloride	Hycamtin®	Lipid-based Capsule 0.25, 1 mg	42 - 70 (pH 1 - 3) 5 (pH 4.5) 0.3 (pH 6.8)	III	32	IaP: 28% IerP: 22%	1.2 – 2.7 mg/m^2 QD: L	2.3 mg/m^2 QD 5 days	Fasted or fed	[121], FDA, EPAR
Toremifene citrate	Fareston®	Physical mixture Tablet 60 mg	0.63 (water) 0.38 (pH 1.7)	I	100	IaP: NA IerP: 32 – 46%	10 – 400 mg QD: L	60 mg QD	Fasted or fed	[30,122,123], FDA, EPAR
Drug substance	**Drug product**	**Formulation and amount of active drug**	**Solubility (mg/mL)**	**BCS/ BDDCS**	**F (%)**	**Variability in-vivo exposure/**	**Dose-proportionality**	**Recommended dose**	**Fed or fasted**	**Reference**

						concentrations **Intra-patient (IaP)** **Inter-patient (IerP)**				
Trametinib dimethyl sulfoxide	Mekinist®	Physical mixture Tablet 0.5, 2 mg	0.0003 (pH 1.2 - 8)	IV	72	IaP: NA IerP: 28 – 36%	0.125 – 4 mg QD: L	2 mg QD	Fasted	[124], FDA, EPAR
Tretinoin	Vesanoid®	Lipid-based Capsule 10 mg	< 0.1	II	50	IaP: NA IerP: 20 – 155 %	25 – 45 mg/m^2 per day: NL	22.5 mg/m^2 BID 90 days	Fed	[30,125]
Trifluridine	Lonsurf®	Prodrug-Physical mixture Tablet 15, 20 mg	60 (pH 1.2 – 7.5)	III	NA	IaP: 16 – 25% IerP: 61 – 64 %	15 – 35 mg/m^2: NL	35 mg/m^2 BID 5 days	Fed	FDA, EPAR
Vandetanib	Caprelsa®	Physical mixture Tablet 100, 300 mg	0.35 (pH 6.8) 0.008 (water)	II	NA	IaP: 10 – 20 % IerP: 60 %	50 – 300 mg QD: L	300 mg QD	Fasted or fed	FDA, EPAR
Vemurafenib	Zelboraf®	Solid dispersion Tablet 240 mg	< 0.00026 (pH 1 – 4.5) 0.0005 (pH 6.8) 0.0009 (pH 7.5)	IV	NA	IaP: 28% IerP: 45%	240 – 960 mg BID: L	960 mg BID	Fed	[126], FDA, EPAR
Vinorelbine ditartrate	Navelbine®	Co-solvent Capsule 20, 30 mg	0.115 (water) > 1000 (pH 3.5)	IV	36	IaP: 19 % IerP: 20 %	60 – 100 mg/m^2 QW: L	60 – 80 mg/m^2 QW	Fed	[39,127–129], FDA
Vismodegib	Erivedge®	Physical mixture Capsule 150 mg	1 (pH 1) 0.0001 (pH 7)	II	7 – 32	IaP: 27 – 42 % IerP: 40 %	150 – 540 mg QD: NL	150 mg QD	Fasted or fed	FDA, EPAR

Figures

Fig. 1 Number and percentage of formulation types of currently licensed orally administered oncolytics in Europe registered on 04-09-2016 (see also Table 3)

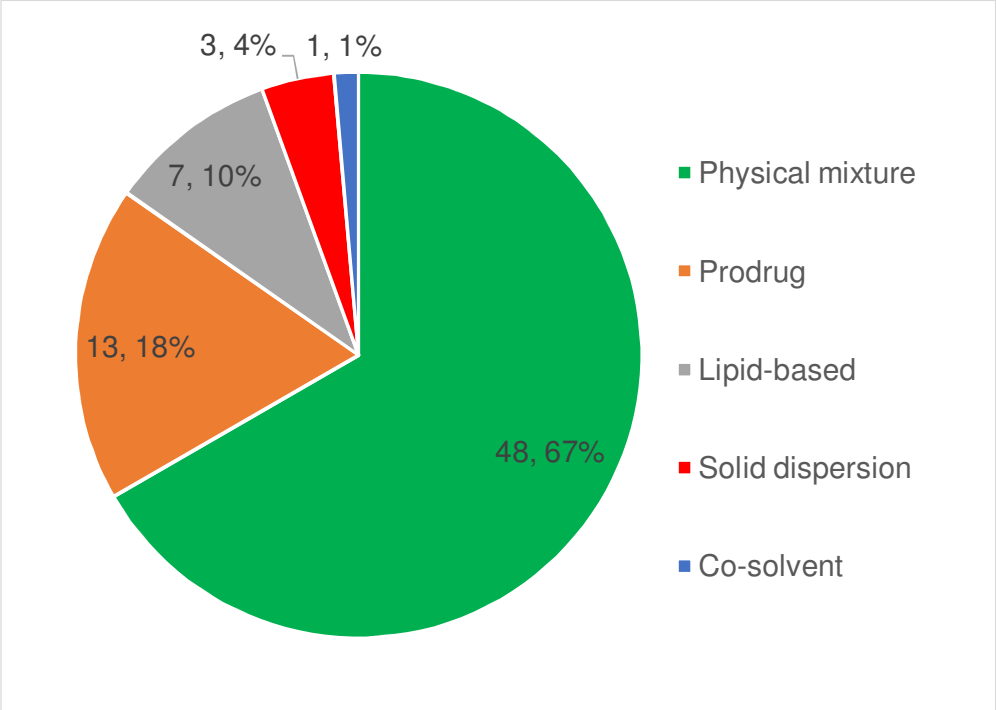


Fig. 2 The pharmaceutical processes of a tablet and a capsule in the gastro-intestinal tract containing a physical powder mixture. A tablet or a capsule enter the gastro-intestinal tract and water (blue color) triggers their disintegration. Capsules contain loosely packed powder which comes in contact with water once the capsule shell is disintegrated. Tablets are first disintegrated into large powder clumps (powder agglomerates) and then to small powder particles. Finally the small powder particles disintegrate to individual molecules. Solvation occurs when water molecules surround drug molecules and this leads to drug dissolution. Only dissolved drug molecules can be absorbed into the bloodstream (red).

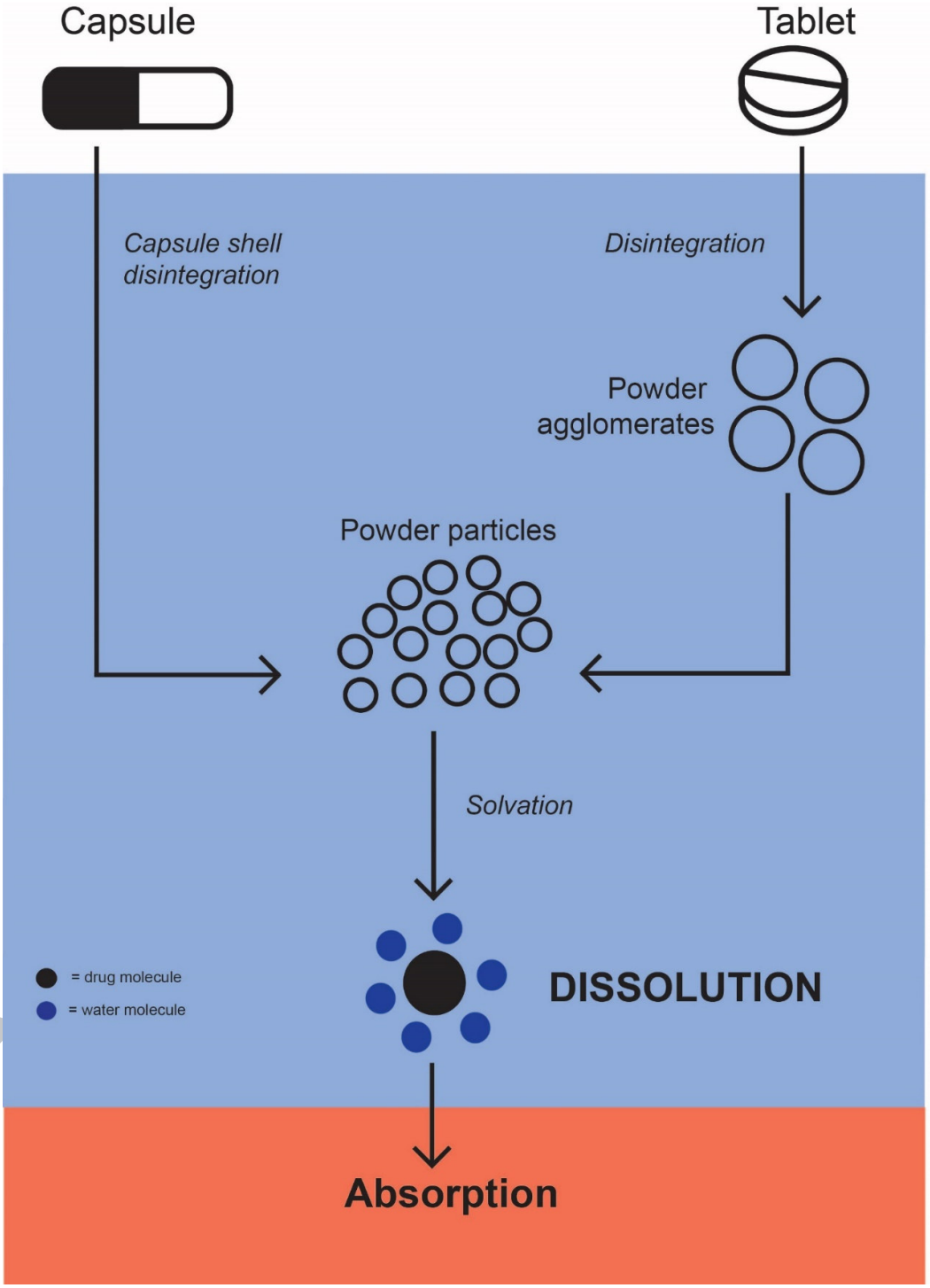
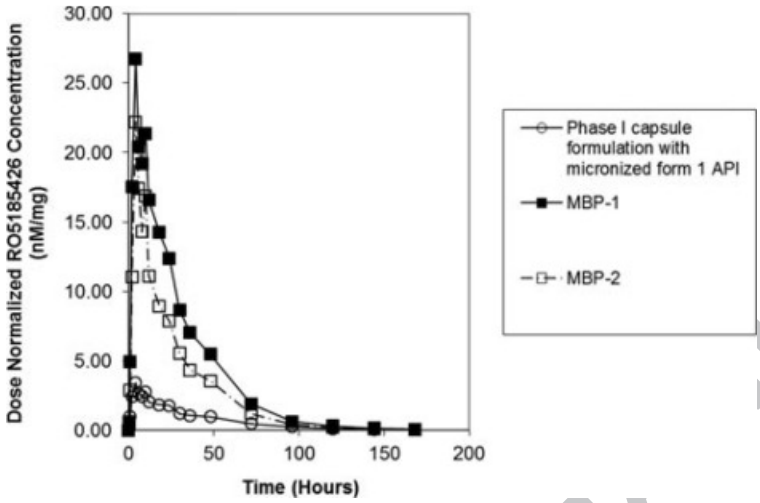


Fig. 3 Example of the impact of a solid dispersion formulation on the plasma concentration-time profile of a low solubility orally administered oncolytic, in this case vemurafenib (RO5185426). MBP = microprecipitated bulk product = vemurafenib solid dispersion. MBP-1 and MBP-2 formulations contain the same vemurafenib solid dispersion but differ in the way the solid dispersion is mixed with capsule excipients: MBP-1 is dry-granulated while MBP-2 is wet-granulated. The solid dispersion formulation resulted in approximately 5 times higher vemurafenib plasma concentrations. Plasma concentrations were similar for MBP-1 and MBP-2. Further clinical development continued with MBP-1. Reprinted from Shah et al [13] with permission from Elsevier.



Inventory of oral anticancer agents: pharmaceutical formulation aspects with focus on the solid dispersion technique

E. Sawicki[a], J.H.M. Schellens[b,c], J.H. Beijnen[a,b,c] and B. Nuijen[a]

Highlights

- This review discusses drug dissolution from a pharmaceutical formulation and focuses on the solid dispersion technique.
- There are currently 72 oncolytics licensed as an oral formulation in Europe, the majority of them are crystalline physical mixture formulations. 3 oral oncolytics are licensed as a solid dispersion: vemurafenib, regorafenib and everolimus.
- In 47% of currently licensed oral oncolytics, poor dissolution contributes to low and unpredictable absorption. For these oncolytics there seems to be room for improving the formulation and a solid dispersion could be considered.

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Conflict of interest

B. Nuijen, J.H. Beijnen and J.H.M. Schellens have a patent in oral taxane formulations. J.H. Beijnen and J.H.M. Schellens are employees and stockholders of Modra Pharmaceuticals BV, a spin-off company developing oral taxanes formulated as a solid dispersion.

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