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Variability in bioavailability of small molecular tyrosine kinase inhibitors



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ABSTRACT

Small molecular tyrosine kinase inhibitors (smTKIs) are in the centre of the very quickly expanding area of personalized chemotherapy and oral applicability thereof. The number of drugs in this class is rapidly growing, with twenty current approvals by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). The drugs are, however, generally characterized by a poor oral, and thus variable, bioavailability. This results in significant variation in plasma levels and exposure. The cause is a complex interplay of factors, including poor aqueous solubility, issued permeability, membrane transport and enzymatic metabolism. Additionally, food and drug–drug interactions can play a significant role. The issues related with an impaired bioavailability generally receive little attention. To the best of our knowledge, this article is the first to provide an overview of the factors that determine the bioavailability of the smTKIs.

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Introduction

The development of anticancer drugs is a very quickly expanding area in which two trends are clearly present. In the first place new agents are designed fulfilling the requirements for personalized medicine. The advancement of techniques such as (cell-based) high throughput screening and the diverse possibilities in molecular modeling have lead to a therapeutic target-based drug discovery regime [1,2]. Along with the evolution of synthetic methods, compounds are found that are highly specific and demonstrate great affinity for molecular targets [3–6]. Individual tumors, and their specific targets, can be genetically characterized and a suitable ‘personalized’ chemotherapy can be appointed depending on the neoplasm’s genotype [7]. The second movement is also referred to as ‘the intravenous to oral switch’. The last decade has shown an increasing number of anticancer drugs that are administered orally [8,9]. Currently, most of the anticancer drugs that are in development or recently approved are destined for oral ingestion. Unlike previous conventions, oral therapy in cancer has proven efficient and less costly [10]. On top of that comes the preference of the patient, especially since oral ingestion can take place in the home setting and is highly convenient compared to intravenous administration [8].

In the middle of these trends stands a promising and growing group of drugs; the tyrosine kinase inhibitors (TKIs). In the past ten years, the size of this group has doubled [11–13]. The TKIs target specific parts of tyrosine kinase receptor proteins that play an important role in the intracellular signaling pathways in tumor cells. Their interference leads to a deregulation of essential cell functions such as proliferation and differentiation [14]. One of the two types of TKIs, the small molecular TKIs (smTKIs) with an intracellular activity, are without exception administered orally. Currently, twenty of these small molecular compounds are approved by both the EMA and the FDA. General information on the drugs is found in Table 1 [11,12]. This review will focus on these particular compounds. The other type of TKI is a group of monoclonal antibodies, which possess a larger molecular structure and interfere with signal transduction by binding extracellularly and are administered intravenously. The small molecular inhibitors have proven useful in the therapy of certain types and lines of cancer [6,11,12,15]. Additionally, smTKIs may be prescribed as alternatives when other therapeutic options have failed or are not appropriate. Although the development of personalized oral chemotherapy is very promising, the nature of the selection process leads to drugs, however, that are hindered by a low and variable bioavailability (*F*). This aspect and its causes are underexposed subjects in literature. Indeed, smTKIs may be very potent and suitable for certain tumor types. When they are unable to reach their target in sufficient quantities, the therapy will be suboptimal or

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Table 1

Overview of the general information on tyrosine kinase inhibitors approved for use by the EMA and the FDA by 1 November 2014.

Drug	Trade name	Primary indication(s)	Oral bioavailability (%)
Afatinib	Giotrif	NSCLC	– ⁴
Axitinib	Inlyta	RCC after failure with sunitinib/ cytokines	47–58
Bosutinib	Bosulif	CML when imatinib, nilotinib and dasatinib are not appropriate	–
Cabozantinib	Cometriq	MTC	–
Crizotinib	Xalkori	NSCLC	43
Dabrafenib	Tafinlar	Melanoma	95
Dasatinib	Sprycel	CML	–
Erlotinib	Tarveca	NSCLC, pancreatic cancer	60–76
Gefitinib	Iressa	NSCLC ¹	57–59
Imatinib	Gleevec/ glivec	CML, ALL, CEL, HES, MDS/MPD, GIST, DFSP	98
Lapatinib	Tyverb	HER-2+ breast cancer	–
Nilotinib	Tasigna	CML	30
Pazopanib	Votrient	RCC, STS	14–39 [163]
Ponatinib	Iclusig	CML when imatinib, nilotinib and dasatinib are not appropriate, ALL ²	–
Regorafenib	Stivarga	CRC, GIST	69–83
Ruxolitinib	Jakavi	CIM, PPVM, PETM	95 ⁵
Sorafenib	Nexavar	HC, RCC, DTC	–
Sunitinib	Sutent	GIST, MRCC, pNET	–
Vandetanib	Caprelsa	MTC ³	–
Vemurafenib	Zelboraf	Melanoma	–

ALL, acute lymphatic leukemia; CEL, chronic eosinophilic leukemia; CIM, chronic idiopathic myelofibrosis; CML, chronic myeloid leukemia; CRC, colorectal cancer; DFSP, dermatofibrosarcoma protuberans; DTC, differentiated thyroid carcinoma; GIST, gastrointestinal stromal tumours; HC, hepatocellular carcinoma; HES, hypereosinophilic syndrome; MDS, myelodysplastic disease; MPD, myeloproliferative disease; MRCC, metastatic renal cell carcinoma; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; PETM, post essential thrombocythaemia myelofibrosis; PPVM, post polycythaemia vera myelofibrosis; pNET, pancreatic neuroendocrine tumours; RCC, Renal cell carcinoma; STS, soft tissue sarcoma.

¹ Withdrawn in 2005 due to lack of evidence in prolongation of life. Source: European Public Assessment Reports (EPARs), Website FDA and Summaries of product characteristics (SmPCs) of the above mentioned smTKIs, accessed at 20th November 2014.

² Changes in usage are suggested by EMA due to life-threatening vascular events.

³ Approval by EMA was conditional.

⁴ Data were not available.

⁵ Based on a mass balance study.

even failing. This review will address the bioavailability-determining factors for the smTKIs and presents prerequisites in both the marketed formulations and chemotherapeutical practice to minimize the reduction and variation in oral *F*. It is important to be aware of and understand the various factors that determine *F* and its variability of the smTKIs. This will allow for the betterment of their use in chemotherapy.

Oral bioavailability

The fraction of the total ingested drug that reaches the systemic circulation unchanged, and is transported to its therapeutic target, is defined and termed (absolutely) bioavailable (*F*) [16]. Fig. 1 schematically presents the different processes that govern the extent of *F*. *F* is the product of the drug fraction that is absorbed (*F_a*), the dose that reaches the hepatic portal vein unchanged (*F_G*) and the fraction of the dose that is not metabolized by enzymes in the liver (*F_H*), as presented in Eq. (1) [16,17],

$$F = F_a * F_G * F_H \quad (1)$$

In each of the before mentioned steps, an amount of drug might be lost. Whatever the cause, a low *F* is associated with an increased intra- and interpatient variability in drug plasma concentration

[18]. Registration texts and other studies, as far as could be accessed, show significant inter-individual variation in important pharmacokinetic parameters of all smTKIs [19–37]. This may result in possibly dangerous situations for patients that experience extensively low, or high, exposure to the substances. Many anticancer drugs are known to exhibit a small therapeutic window, where the minimum therapeutic dose and the maximum tolerated dose (MTD) are close to each other [38]. The same is true for the smTKIs, with a possible exception of Dabrafenib, Imatinib, Gefitinib and Pazopanib [13,19,39–52]. As a consequence of pharmacokinetic variation, inter-individual differences in therapeutic dose and MTD should be taken into account. Under- and overdosing are thus potential hazards of oral chemotherapy. Thus, careful dose titration and adjustments are required to assure an adequate therapy, in both effect and tolerance. Hence, therapeutic drug monitoring (TDM) is upcoming for smTKIs [38].

The human oral *F* of the smTKIs is largely unknown or inaccessible in the public domain and published values are generally low and the exposure is variable [39,53,54]. The determination of oral *F*-values requires a comparison between oral and IV-administration. IV-solutions with smTKIs are often difficult to prepare due to the poor water solubility of the drugs (see Section 'Dissolution'). Table 1 presents the currently known values. Low values for oral *F* may be due to one or more of several factors. It is often the consequence of a complex interplay of both physicochemical and physiological processes. Furthermore, it may also be influenced by concomitant administration of other drugs. Additionally, the intake of food or certain habits of life-style may exert an impact on *F*.

B(DD)CS-classification

The Biopharmaceutics Classification System (BCS) can aid to clarify possible absorption-related causes of an impaired *F*. Solubility and permeability of a drug are recognized as fundamental parameters in the absorption process [55]. The BCS combines data on the *in vitro* solubility in the intestinal tract of the drug substance and data on the extent of total permeation through the gut wall and appoints a class to it [55–57]. Fig. 2 summarizes the assignment of the classes and presents the classes of the smTKIs [58,59,37]. Classifications may be interpreted as signals for formulation design (class II and IV) or physicochemical modifications (class III and IV) [58].

The newer Biopharmaceutics Drug Disposition Classification system (BDDCS) correlates the passive permeability rate of drug with their metabolic elimination [60–62]. Here, passive permeability is considered 'good' when elimination is largely governed by metabolism (>70%) [63]. Fig. 2 presents the BDDCS classification between braces where it differs from the BCS classification. The discrepancies between the BCS and BDDCS classes may be due to the fact that BCS is based on total permeation and BDDCS on the passive permeability rate [64]. The latter does not account for interaction with membrane transporters.

Pharmaceutical factors (*F_p*)

Dissolution

The first step in becoming bioavailable is the dissolution of the drug substance into the gastrointestinal fluids. Since only the solute form of the drug can be absorbed, the release from the oral formulation is an important parameter. In fact, the major cause for the different absorption profiles of drugs from various products is

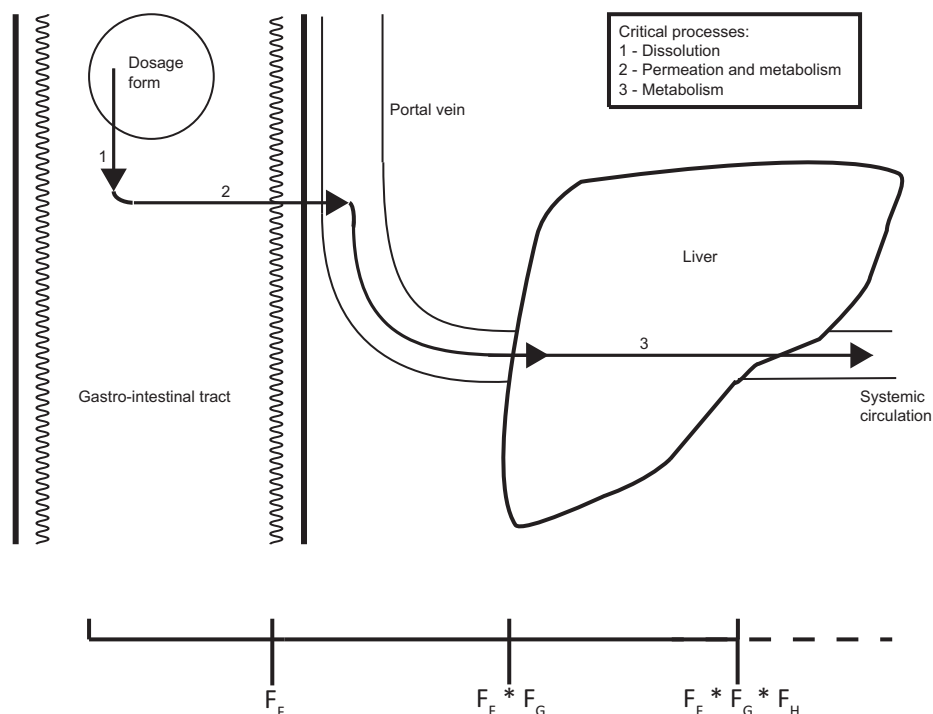


Fig. 1. Schematic overview (simplified) of major bioavailability determinants and corresponding fractions (bottom scale).

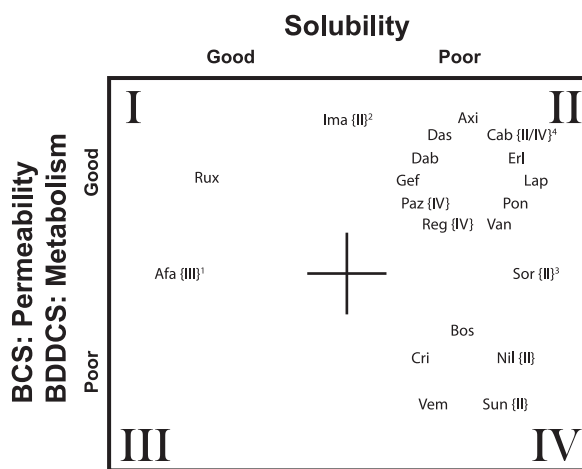


Fig. 2. The Biopharmaceutics Classification System (BCS) as proposed by Amidon et al. [56]. and the Biopharmaceutics Drug Disposition Classification System (BDDCS) as proposed by Wu et al. [61]. B(DD)CS classifications of smTKIs indicated with three-letter abbreviations. ¹I/III; *in vitro* data were inconclusive. ²I/II; inconclusive solubility data. ³II/IV; conflicting permeability data. Source: EPARs, additional sources indicated where appropriate.

dissolution [16]. The dissolution rate of a drug substance can be described using the Noyes-Whitney equation (Eq. 2) [65,66]:

$$\frac{dW}{dt} = D * A * \frac{C_s - C}{h} \quad (2)$$

in which dW/dt is the dissolution rate (mg/min), D the diffusion coefficient (cm^2/min), A the surface area of the dissolving compound (cm^2), C_s the saturation concentration (concentration in the diffusion layer, mg/L), C the concentration in the solvent (mg/L) and h the thickness of the diffusion layer (cm) [66].

The diffusion coefficient and the thickness of the diffusion layer are dependent on highly variable patient parameters, such as

gastrointestinal pH and viscosity [67–69]. Certain excipients in formulations may be used to manipulate drug diffusivity [70]. These are not found in smTKI formulations. The following will discuss solubility and surface area, which are both most frequently modified in formulations of smTKIs.

Solubility

The degree of a compound's solubility is dependent on physico-chemical factors of the solute and the solvent. The gastrointestinal fluids are aqueous and therefore, the water solubility at various pH-values of a drug is used to predict its apparent solubility in the GI-tract [71]. The small intestine has the greatest of surfaces of the organs in the gastrointestinal tract. It is here where most of the smTKIs are considered to be absorbed. The transit time of materials in the small intestine is approximately 3–4 h [72], in which the absorption must take place. For these reasons, drug solubility in the small intestine is a prerequisite.

The pH value in the intestinal lumen rises from pH 2 near the stomach to pH 5–6 in the jejunum, ending at pH 7–8 near the ileocecal valve [73]. The acidity of the GI-fluids greatly influences the solubility of the smTKIs. Most of the smTKIs are weak bases (pK_a -values in Table 2) which are protonated, and as such most soluble, in acidic environments [74]. The increase in pH-values encountered in the intestines dramatically decreases their solubility [75]. The result of this is a relative high solubility in the stomach, but a significantly lower one in the intestinal lumen. Consequently, the basic compounds classify as B(DD)CS II or IV, due to this issued solubility at higher pH-values. Another explanation for the poor solubility behavior is the general high lipophilicity of the smTKI group [11,76]. Based on structural similarity it is reasonable to assume that the group as a whole has a lipophilic character. Ruxolitinib stands out from the rest; it is relatively water-soluble [11].

Salt formation improves water solubility of compounds, either acidic or basic, because it allows the substances to dissociate in hydrated ions [77]. Salt forms of the marketed formulations are presented in Table 2 [11,19]. The choice of the counterion is not

Table 2

Overview of physical characteristics of the commercially available dosage forms of the smTKIs.

Drug	Commercial salt form (crystal state ¹)	pK _a	Reference
<i>Tablet formulations</i>			
Afatinib	Di-maleate (A)	5.0, 8.2	[21]
Axitinib	Free base (XLI)	4.8	
Bosutinib	Monohydrate (1)	n.a.	
Dasatinib	Monohydrate (H1–7)	3.1, 6.8, 10.8	[164]
Erlotinib	Hydrochloride (A)	5.4	[165]
Gefitinib	Free base ²	5.4, 7.2	
Imatinib ⁴	Mesylate (beta/amorphous ³)	1.5–8.1	
Lapatinib	Ditosylate monohydrate ²	n.a.	
Pazopanib	Hydrochloride (1)	2.1, 6.4, 10.2	
Ponatinib	Hydrochloride ²	2.8, 7.8	
Regorafenib	Co-precipitate (amorphous)	n.a.	[166]
Ruxolitinib	Phosphate anhydrate ²	4.3, 11.8	
Sorafenib	Tosylate (I)	n.a.	
Vandetanib	Free base ²	5.2, 9.4	
Vemurafenib	Co-precipitate (amorphous)	7.9, 11.1	
<i>Capsule formulations</i>			
Cabozantinib	L-malate (N-2)	n.a.	[166]
Crizotinib	Free base (A)	5.6, 9.4	
Dabrafenib	Mesylate (1)	2.2, 6.6	
Nilotinib	Hydrochloride monohydrate (B)	2.1, 5.4	
Sunitinib	Malate (I)	8.9	

¹ Names of polymorphisms presented as in the texts of EPARs and/or patents.

² Data on polymorphisms not available.

³ Generic formulations contain either of both.

⁴ Both tablet and capsule formulations marketed. Source: EPARs and FDA chemistry reviews, additional sources indicated where appropriate.

only based on solubility but also with regard to the stability of the compound and its tendency to be hygroscopic [78,79].

Many of the smTKIs exhibit crystalline polymorphism [11,19,76]. The particular crystal structure chosen for the pharmaceutical product offers the best combination of stability and solubility. Besides crystal structures, solid compounds can arrange themselves in a more loosely-ordered amorphous state [80]. The advantage of the amorphous form is the higher apparent solubility, owing to the high levels of supersaturation in aqueous media [81]. This form is thermodynamically unstable relative to the crystal and generally has a tendency to revert back to a crystal form [82]. The amorphous form must thus be stabilized by the formulation that contains it. Regorafenib and vemurafenib were found to be poorly soluble in any of the investigated crystal forms. The marketed tablets with these compounds hold solid solutions with amorphous states of the drugs [11]. Table 2 lists the crystal polymorphisms used in the marketed formulations. It has been proposed that hydroxypropyl methylcellulose (HPMC) may inhibit dabrafenib precipitation *in vivo* [83] by maintaining supersaturation. This could possibly be the case with other capsulated smTKIs as well.

Surface area

The surface area of the compound in contact with the solvent is directly proportional to the dissolution rate [84]. It can be manipulated by increasing or decreasing particle size. Smaller particle sizes do not only demonstrate a higher dissolution rate due to the enlarged surface area. A more efficient wettability or wetting, the degree with which the drug comes into contact with the solute, also contributes [85]. As far as could be assessed, it was found that size distribution of the drug particles in the commercialized formulations of the smTKIs were optimized in relation to dissolution properties [11]. Further formulation modifications were made to tablets to ensure a fast and complete disintegration,

enhancing the *in vivo* surface area. Five of the smTKIs are marketed as capsules. The capsules contain a powdered formulation that rapidly wettens when it comes in contact with the gastrointestinal fluids [11]. Table 2 summarizes the oral dosage forms of the smTKIs.

Physiological factors (F_C & F_H)

Permeability and passive transport

The degree of permeability describes the extent of (intestinal) membrane penetration of a drug [86]. The passing of molecules occurs through passive or facilitated diffusion, (active) carrier mediated or paracellular transport [87,88]. Lipophile, large and relatively uncharged drugs are moved transcellularly through cell membranes. This passive transport is a or the major route of movement across membranes of many drugs [86,89]. The same is reported for the smTKIs, although this is not expressibly described. Support for this is found in the fact that most smTKIs are classified as class I or II in the BDDCS (Fig. 2). Considering the lipophile molecular structure of the smTKIs, transcellular transport seems the most probable route for passive movement [11,76].

Carrier-mediated transport

One of the physiological factors that can have a great impact on the absorption from the intestinal lumen is the presence of membrane drug transporters [90,91]. The intestinal epithelial lining expresses a large number of transporter proteins [92]. Two major superfamilies, the ATP binding cassette (ABC) transporters and the solute carrier (SLC) transporters, are located in the intestinal wall [93,94]. Transporters can either facilitate uptake or by efflux from the intestinal cells back into the intestinal lumen [90,95].

A subfamily of the SLC transporter, the organic anion transporting proteins (OATPs) is expressed in the small intestine in several isoforms [96,97]. The OATP group of transporters provides mediation for ionic agents in their intestinal absorption, which results in a higher uptake rate than would be expected diffusion-wise. Most

Table 3

Demonstrated substrate specificity of major intestinal transporter proteins for smTKIs and demonstrated enzyme interactions of smTKIs.

Drug	Transporters	Enzymes	Reference(s)
Afatinib	P-gp, BCRP	–	[167]
Axitinib	OATP, P-gp, BCRP	3A4/5, 1A2, 2C19, UGT	[168,169]
Bosutinib	P-gp	3A4	[23,170]
Cabozantinib	– [*]	3A4, 2C8	[171]
Crizotinib	OATP, P-gp	3A4/5	[172,173]
Dabrafenib	P-gp, BCRP	3A4, 2C8	[24]
Dasatinib	OATP, P-gp, BCRP	3A4	[172,174]
Erlotinib	P-gp, BCRP	3A4/5, 1A2	[25,175,176]
Gefitinib	P-gp, OATP, BCRP	3A4/5, 2D6	[172,175,177]
Imatinib	P-gp, OATP, BCRP	3A4	[172,178,179]
Lapatinib	P-gp, OATP, BCRP	3A4/5, 2C19, 2C8	[180,181]
Nilotinib	P-gp, OATP, BCRP	3A4	[172]
Pazopanib	P-gp, OATP, BCRP	3A4, 1A2, 2C8, UGT	[172,163]
Ponatinib	P-gp, BCRP	3A4	
Regorafenib	–	3A4, UGT	[13]
Ruxolitinib	–	3A4	[182]
Sorafenib	OATP, P-gp, MRP-2, BCRP	3A4, UGT	[172,183–186]
Sunitinib	OATP, P-gp, BCRP	3A4	[172,187,188]
Vandetanib	OATP, P-gp, BCRP	3A4	[172,189,190]
Vemurafenib	OATP, P-gp, BCRP	3A4	[172,191,192]

^{*} Research ongoing or data not available. Source: EPARs and FDA label texts, additional sources indicated where appropriate.

of the smTKIs have been reported to be substrates of an isoform of OATP, although clinical relevance has not been established [11,12], Table 3.

Of special interest are the ATP binding cassette (ABC) transporters, since these are most abundant and most of the smTKIs are substrates of these proteins. The ABC-transporters can be subdivided into three families that are involved in the transport of anti-cancer drugs in the intestines: permeability-glycoprotein (P-gp), the multidrug resistance-associated proteins (MRP) and the breast cancer resistance protein (BCRP) [98].

P-gp transporters are present in the membranes of cells throughout the entire human body. It is believed to have a function in removing toxins and metabolites out of cells [95]. The presence of P-gp in the membrane on the luminal side of the gut wall can prove troublesome for drug absorption. It functions as an efflux pump with a broad substrate range with an overall preference for hydrophobic and amphipathic molecules. It includes most of the smTKIs, as listed in Table 3.

The MRP transporter family has one principal member (MRP 2) expressed on the luminal side of the intestinal wall [99]. The substrate range includes, but is not limited to, organic anions. It functions in very much the same fashion as P-gp does, it pumps toxins and foreign drug molecules from the intestinal cells back into the lumen. Table 3 presents the known smTKI substrates of MRP 2.

BCRP transporters align with P-gp and MRP proteins in efflux function [100]. BCRP is present in both the small and the large intestine and its expression does not vary significantly per location [101]. The transport is also involved in the development of resistance to several classes of chemotherapeutics [102]. It is expressed on the luminal side of the intestinal epithelial cells. The range of substrates of BCRP varies greatly and has been shown to include a number of smTKIs, as presented in Table 3.

As is the case with many substrates, the substrate specificity for smTKIs of the different efflux transporters overlaps for some substrates [11,12]. This can lead to a synergistic effect of the transporters in limiting drug penetration across the intestinal barrier [90].

Metabolism

Metabolism is the major mechanism for elimination of drugs from the body [103–105]. The typical metabolic steps include oxidation, reduction, hydrolysis and conjugation. The first three are often referred to as phase I reactions and the latter as phase II, owing to the order in which the reactions frequently occur. Drugs can be metabolized before they reach the systemic circulation (first-pass metabolism) and after distribution through the body. Metabolism may render drug molecules inactive. On the other hand, metabolites may exhibit lower, higher or equivalent bioactivity compared to the parent compound [106]. The intestinal wall and the liver are responsible for the first-pass metabolism. Respectively, these organs determine the gastrointestinal and the hepatic *F*. Many of the enzymes involved in phase I and II reactions are present in both the liver and the gut wall, albeit that the liver generally contains larger amounts [107].

Cytochrome P450 (CYP) enzymes are responsible for the majority of phase I metabolism of a enormous variety of exogenous and endogenous compounds [108]. It is estimated that 80% of the oxidative metabolism of drugs can be attributed to CYP enzymes [109]. The isoenzymes of the CYP-superfamily are classified based of structure into families and subfamilies [110]. The liver contains the most diverse collection of CYP enzymes and possesses the highest drug-metabolizing activity. The intestinal wall also contains an array of CYP enzymes and can substantially contribute to the first-pass metabolism [107]. *In vitro* and some *in vivo* studies have shown that CYP-enzymes play a role in the metabolism of all

smTKIs [11,12], except for afatinib that does not seem to be metabolized in the human body to relevant extent. Table 3 presents an overview of the isoenzymes that are primarily involved in the metabolism of smTKIs. In addition to CYP metabolism, glucuronidation by UDP-glucuronosyltransferases (UGTs) is an important clearance pathway [111,112]. This phase II reaction is present in more than 80% of the metabolic pathways of drugs [113]. The enzymes are present in various tissues including intestines and liver. Table 3 presents the smTKI substrates for UGT.

Drugs, the smTKIs themselves and other substances present in food and drinks can exhibit an influence on the number and functions of membrane transporters and metabolizing enzymes [114]. Concomitant use of an inducer or inhibitor of these proteins can significantly affect the absorbed dose of substrate smTKIs, ingestion of grapefruit juice is such an example [115–117]. An increasing list of inducers and inhibitors can be found in literature [114,118]. Another variable is genetic polymorphism. Inter- and inpatient variability may be observed because of different expression patterns of transporters and enzymes. A major factor here is genetic predisposition of patients where ethnic background is important [119–121]. A growing body of evidence suggests that genetic polymorphism may play an important role in determining smTKI plasma concentration [11,12,122]. However, the clinical significance of pharmacogenetics in smTKI therapy still need to be proven in adequately set-up studies [123–125].

Special populations

Elderly

The process of aging involves changes in physiology and the functioning of organ systems. Important hepatic changes when considering drugs are a decrease in liver mass and CYP450 content. Kidneys decrease in mass with age and renal blood flow lessens. Gastric motility slows down and the secretion of gastric juices decreases [126]. Cancer is generally considered to be a disease of the elderly, with 60% of the diagnoses of cancer taking place in patients aged 75 and over [127]. Although age-induced *F* alterations seem possible, literature and registration texts do not report the necessity of adjusting the dose of smTKIs for the elderly [11–13].

The hepatic impaired

The major site of drug metabolism and excretion for smTKIs is the liver. Liver function and hepatic impairment may have a clinically significant influence on the levels of the smTKIs. Liver cirrhosis, a key outcome of hepatic impairment, can be classified using various methods. The FDA wields the Child-Pugh classification (CPC) in their label texts, and so will this review. The CPC applies three classes (A, B and C) in increasing severity and clinical prognoses [128]. Serologic data, e.g., serum albumin and prothrombin time are the basis for this classification. Table 4 presents the dose adjustments that need to be taken when hepatic impairment has been diagnosed for different CPC-scores. For most of the smTKIs at most of the different stages of the CPC-scale, no change dosage is recommended. Careful surveillance during therapy is required however, since clinical data upon which dose recommendation are stated are often from small scale studies. Hepatic impairment studies are generally carried out using non-cancer patients. Cancer and chemotherapy may induce additional changes in physiology of the liver, directly or indirectly [129–132]. Both lead to a reasoning where individual patient levels may need to be monitored in cases of (suspected) hepatic impairment.

Table 4

Dose adjustment advice for the smTKIs in the different stages of the Child-Pugh liver impairment scale.

Drug	A	B	C
Afatinib	↔	↔	?
Axitinib	↔	↓	?
Bosutinib	↓	↓	↓
Cabozantinib	↔	X	X
Crizotinib	?	?	?
Dabrafenib	?	?	?
Dasatinib	↔	↔	↔
Erlotinib	↔	↔	↔
Gefitinib	↔	↔	↔
Imatinib	↔	↔	↓
Lapatinib	↔	↔	↓
Nilotinib	↓	↓	↓
Pazopanib	↔	↓	X
Ponatinib	?	?	?
Regorafenib	↔	↔	X
Ruxolitinib	↓	↓	X
Sorafenib	↔	↔	?
Sunitinib	↔	↔	?
Vandetanib	↔	X	X
Vemurafenib	↔	↔	↔

↔, No dose adjustment required; ↓, dose should be reduced; ?, effects not studied; X, do not use. Source: FDA label texts.

Selected interactions

Food

The ingestion of food can cause the *F* of co-ingested drugs to change. The mechanisms by which this happens are not fully understood, but some clarification may be obtained from physiological changes caused by the presence of food [133,134]. The pH-values in the gastric environment may rise from 1–3.5 to 3.0–6.0 due to buffering and dilutant effects of food stuffs [135]. The proximal part of the duodenum does experience lower pH values when gastric emptying takes place [136]. Overall, fluctuations because of food in pH of the intestinal system are reported to be less dramatic and may cause the pH to lower by 1 [137]. Both are subject to inter- and intra-individual variations [138]. The presence of fat in food slows gastric emptying and such prolongs the residence time in the stomach [139,140]. Food triggers the gastro-colonic reflex, which speeds the motility in the terminal ileum and caecum [141]. The third important change is the composition of the gastrointestinal fluids. In the fed-state, the fluids exhibit higher buffer capacities, higher osmolality and higher concentrations of short-chain fatty acids and bile salts [142]. Any of these changes may affect the absorption of drugs from the GI-tract. Fluctuations in pH may change solubility and charging of compounds, in- or decreasing the dissolution rate [143]. Motility directly determines the maximum time available for absorption [144]. The fluid composition might lower the diffusion of compounds due to an increased osmolality or could increase solubility by dissolution of drug in fat or by bile salt emulsification [67].

There are no studies at present that have examined the mechanisms by which the absorption of smTKIs are influenced by food. The effects, however, are known for all the compounds. The smTKIs show a varying change in absorption when fasting and fed-state are compared. Clinical advice on administration timing can be given in situations where adequate evidence is available on food effects. The nature of the advice will depend on the effect of the food on the therapy and whether such an effect is beneficial. An advice to administer a smTKI without food should be interpreted as ingesting a tablet or capsule at least two hours after a meal or one hour before meal consumption [11,12]. Table 5 presents the influence food has on the absorption of smTKIs and lists

Table 5

Effect of food and acid regulation drugs on smTKI absorption and administration advices.

Drug	Food		Antacids		Reference(s)
	Exposure (AUC)	Advice	Exposure	Advice	
Afatinib	–39%	WO	↔	–	[193]
Axitinib	+19%	WO/F	↔	–	
Bosutinib	+70%	F	↓	A	[194]
Cabozantinib	+57%	WO	(↓) ¹	–	[195]
Crizotinib	–14%	WO/F	(↓)	–	
Dabrafenib	–31%	WO	(↓)	–	
Dasatinib	+14%	WO/F	↓	A	
Erlotinib	+109%	WO	↓	A	[196,197]
Gefitinib	–14 to +37%	WO/F	(↓)	A	
Imatinib	?	F ²	↔	–	[146]
Lapatinib	+80–161%	³	↓	A	
Nilotinib	+29–82%	WO	↓	A	[198]
Pazopanib	+100%	WO	↓	A	
Ponatinib	–3 to +9%	WO/F	(↓)	A	[199]
Regorafenib	+36–48%	F	(↔)	–	[200]
Ruxolitinib	?	WO/F	↔	–	
Sorafenib	–29 to +14%	WO	(↓)	A	[147]
Sunitinib	+12%	WO/F	(↓)	–	
Vandetanib	?	WO/F	(↓)	–	[147]
Vemurafenib	+200%	WO/F ⁴	?	? ⁴	

↑, Increased exposure; ↓, lowered exposure; ↔, no effect; ?, unknown effect; (↑)/(↓) (↔), possible effect; –, no avoidance needed; A, avoidance needed. WO, without food; F, with food. Source: EPARs and FDA label texts, additional sources indicated where appropriate.

¹ No formal studies done.

² Food serves as gastrointestinal protection.

³ 1 h before or after meal (see text).

⁴ Advice not (yet) given.

the advices giving by the EMA and FDA on administration in fed or fasted state.

Bosutinib is preferably given in the presence of food, an increase in tolerability of bosutinib was observed compared to the fasting-state [145]. Regorafenib should be combined with the intake of a low-fat meal, which increases the exposure of the drug and its active metabolites compared to fasting-state and high-fat meal [12,13]. Lapatinib exhibits a four-time increase in exposure during fed-state in comparison with fasting-state. It is advisable to give lapatinib somewhere in a window of 1 h before or after a meal, but preferably before [146]. To maintain constant blood levels, this should be standardized for the individual patient. It was chosen to advise the intake of imatinib with food to minimize adverse reactions in stomach as food shields the stomach and esophagus lining [12]. The food effect on vemurafenib has only very recently been studied. The authorities did not issue an advice concerning food intake yet. A conclusive advice needs to be constructed after thorough interpretation of the study results [147].

Stomach pH regulating drugs

Drugs that have an effect on the acid secretion and the pH-value of the stomach are abundantly prescribed and bought as over-the-counter (OTC) products [148,149]. Dyspepsia and related gastrointestinal disorders have been reported as adverse reactions following therapy with smTKIs [11,12,150–152]. Treatment options are the use of antacids, histamine H2 receptor antagonists and proton pump inhibitors (PPIs) [149].

The pH increasing drugs neutralize or reduce gastric acid by different mechanisms and are administered in various dosing schemes with PPIs as the most effective and most popular [11,12,153,154].

For most of the smTKIs it has been well established whether they suffer from a change in absorption caused by concomitant

therapy with a pH-changing drug. pH-dependent solubility plays a crucial role in these interactions. Absorption of drugs may decrease when the pH is increased in the gastric environment [149,155,156]. When this is the case, the advice to avoid the effects on the pH-value may be needed.

Different avoidance protocols can be used depending on the type of pH-increasing drug. Antacids should not be administered at the same time as the smTKI. Instead, the smTKI should be ingested two hours before or four hours after the antacid. For both H₂-antagonists and PPIs, one protocol can be applied; the smTKI must be administered along with the pH-increasing drug, or the acid-regulating drugs should be taken in the morning and the smTKI before the night [11,12]. The concomitant administration avoids pH-effects since the pH-regulator has to be absorbed in order to be active and as such, a window of absorbance is provided for the smTKI.

Cabozantinib, crizotinib, dabrafenib, gefitinib, ponatinib, sorafenib, and vandetanib all exhibit pH-dependent solubility. Interaction studies with the pH-regulating drugs have not been performed with regard to these smTKIs, however. On grounds of their physicochemical properties, such interactions may be probable. This has led to the avoidance advice for ponatinib and sorafenib [11,12]. The protocol is not recommended for the other compounds at this point in time. Nevertheless, caution during concomitant use is required since interactions are not ruled out. Table 5 lists the effect of concomitant administration of pH regulators and smTKIs and the avoidance advices.

No statements covering the possible interaction with vemurafenib due to pH-changes are found in literature. The drug is found to be poorly soluble at pH 6.8 in its crystal form. The marketed formulation is comprised of a solid solution that may react differently to changes in pH. The same is true for regorafenib. No substantiated advice can be given for these two drugs, caution, again, is still warranted.

Discussion

The advances in drug discovery have led to a particularly useful niche of chemotherapeutics, the orally applicable smTKIs as key representatives. Although the development of personalized oral chemotherapy is very promising, the nature of the selection process leads to drugs that are hindered by a low and variable F . This low and variable F does not appear to be a hindrance in the wielding of the drugs, but might prove to be troublesome in further expanding the use of these compounds. High or specifically low dosing and frequent multiple dosing regimens may find hurdles here.

Data on the physicochemical properties of the smTKIs is sparsely scattered and largely covered by patents. It is, however, clear that most of the drugs suffer from solubility problems. Marketed formulations only possess the most basic physicochemical adjustments to increase the absorption from tablets and capsules. As has been done with other chemotherapeutics, it may be rewarding to seek novel formulation strategies, such as solid dispersion or self-emulsifying systems [157], to increase solubility. Regorafenib and vemurafenib formulations wield such strategies [11].

In vivo data concerning interactions with intestinal protein transporters and metabolizing enzymes are coming together slowly, but large clinical studies are still to be performed. Interactions with inducers or inhibitors of transporters and enzymes should always be considered during chemotherapy, even though current knowledge on the matter is limited. Once certain enzyme or transporter involvement is deemed clinically relevant, therapy routines or formulations can be combined with an additional inhibitor to decrease enzymatic breakdown or extensive

efflux. The causes for the variable and low F for the smTKIs are slowly being uncovered and more studies are coming along to investigate the drugs further. Current knowledge implies that solubility and metabolism, especially concerning CYP450, play a pivotal role.

Interactions with food are profound. The mechanisms underlying the effect of food on F are not understood in detail. It may be beneficial to study these effects more thoroughly to assess the consequence of different amounts of fats in food. This in turn may prove useful in formulation design, especially when lipid-based formulations are considered [158].

Whatever the value of the F , it is important to keep in mind that it does not give any information about the exposure of the therapeutic target to the drug. A drug that has reached the systemic circulation, even in its entirety, still needs to travel to its molecular target in order to be therapeutically active. In the case of the smTKIs, the targets are the kinases that are located inside the tumor cells and often in endothelial cells in the micro-environment. Various obstacles may be encountered that may sharply reduce or even diminish the amount of drug that reaches its target. An example is the blood brain barrier, which has been shown to be a partial blockade to EGFR-smTKIs [159]. This therapeutic availability (F_{Ther}) can be described by adding a fraction to Eq. (1), the fraction of the bioavailable drug that reaches the therapeutic target (F_T), to yield Eq. (3),

$$F_{\text{Ther}} = F_F * F_G * F_H * F_T \quad (3)$$

Furthermore, patient compliance to therapy is essential in the success of oral cancer treatment. It is estimated that compliance of cancer patients taking oral chemotherapeutics ranges between 20% and 100% [160]. Adverse events are the main cause for a impaired compliance, especially gastro-intestinal side effects are associated with smTKIs [161]. Alternating compliance, although not directly influencing the bioavailability, adds another variable to the mix in determining mean plasma concentrations. For this reason, care should also be placed and directed towards the therapeutic infrastructure. Guidance of patients during the experience of adverse events may prove to be helpful in keeping compliance at a high level [162].

Conclusion

The smTKI-group generally suffers from a low and variable F , a problem that is receiving little attention in literature. This review presents the various causes of the low and variable F of the smTKIs and provides possible means to enhance F and to reduce variability. Special attention is directed towards food and pH-dependent interactions, which have consequences for the therapeutic regimen of most of the smTKIs. Physicochemical, physiological and pharmacological data is far from complete. More and larger scale studies on these matters are needed to clarify the individual contribution to the impaired F of each of the factors. This will allow for adequately directed formulative or therapeutic measures for the enhancement of F .

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