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Review article

Inherent formulation issues of kinase inhibitors

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ABSTRACT

The small molecular Kinase Inhibitor (smKI) drug class is very promising and rapidly expanding. All of these drugs are administered orally. The clear relationship between structure and function has led to drugs with a general low intrinsic solubility. The majority of the commercial pharmaceutical formulations of the smKIs are physical mixtures that are limited by the low drug solubility of a salt form. This class of drugs is therefore characterized by an impaired and variable bioavailability rendering them costly and their therapies suboptimal. New formulations are sparingly being reported in literature and patents. The presented data suggests that continued research into formulation design can help to develop more efficient and cost-effective smKI formulation. Moreover, it may also be of help in the future design of the formulations of new smKIs.

Contents

1. Introduction

Small molecular Kinase Inhibitors (smKIs) form a promising and rapidly expanding class of drugs [1,2]. The drugs target specific parts of Kinase receptor proteins that play an important part in the intracellular growth signaling pathways in tumor and immune cells [3–5]. After the first drug approval by the United States Food and

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Drug Administration (FDA) of Imatinib in 2001 [6,7], the number of drugs approved by both the FDA and European Medicines Agency (EMA) are now nearing 30, listed in Table 1. Many more smKIs are being investigated in clinical trials and are expected to be approved in the coming years. A range of small molecular inhibitors have proven to be useful in the therapy of certain types of cancer. Additionally, smKIs may be prescribed as alternatives when other therapeutic options have failed or are deemed inappropriate [8]. A few compounds are (also) applied in the therapy of immunomodulated diseases [9–12] and may even have a future in the therapy of diseases such as diabetes mellitus [13].

All of the smKIs are without exception administered orally. This has great advantages in terms of patient convenience and cost reduction [14–16]. It presents however serious difficulties for compounds with a low solubility and/or permeability. These drugs are hindered by a reduced and variable bioavailability. This may cause drug plasma concentrations to be ineffectively low or toxically high with all due consequences [17]. Understanding and controlling the parameters of solubility and permeability can therefore have a profound influence on patient plasma drug levels.

The smKIs have been designed using high-throughput screening and combinatorial chemistry from which the intricate structures and inherent solubility issues originate [18]. These means are used in the drug discovery of other drug classes as well, *e.g.* drugs acting on the central nervous system that also experience a problematic solubility [19].

Drug solubility and the dissolution process are affected by a plethora of factors with clinical implications. A number of these factors are inherent to the smKI structure and function. It follows that, as drug dissolution is most often the primary determinant for the smKI bioavailability, there is an apparent link between the high specificity of the smKIs and their impaired absorption into the systemic circulation.

This article will first present the overall problematic biopharmaceutical properties of the smKI drug group. Secondly, it will discuss the characteristic structural elements that are responsible for the solubility behavior of the smKIs. It will continue by reviewing the current commercial formulations along with alternative investigational formulations. This article aims to underline that although high specificity can, in many cases, place a challenging strain on drug solubility and bioavailability, different and innovative formulation techniques may present possible solutions to some of these issues. Literature offers several reviews that address (pre)formulation challenges for poorly soluble drugs in general [20–22]. This article focuses on smKIs in particular. To the authors' knowledge, this review is the first to combine literature and patent research on the solubility and formulation of smKI compounds from a pharmaceutical perspective.

2. Bioavailability

In the process of reaching the therapeutic target, the first step after oral administration and the disintegration of the dosage form is always the dissolution of the drug substance [75]. The second step, absorption, only takes place with the dissolved portion of the drug. Thus, poor drug solubility can be one of the main causes for a low and variable uptake of a drug into the systemic circulation, *i.e.* a low and variable bioavailability. This is generally true for the smKIs, as listed in Table 1. This reflects back in their BCS (the Biopharmaceutical Classification System)-classes of which most are II (solubility hindered bioavailability) or IV (solubility and permeability hindered bioavailability) [76,77].

Factors such as presystemic metabolism and mediated transport by transporter proteins may also play a part in reducing a drug's bioavailability. The combination of these factors is reviewed elsewhere [78,79].

3. Physicochemistry

3.1. Essential structures

In the past few decades the role of signal proteins in the homeostasis of tumors became more and more apparent [80,81]. The advancement of the diverse techniques and possibilities of molecular modelling have led to a therapeutic target-based drug discovery regime [82,83]. With it, structure-activity relations for inhibitory molecules for these proteins were assessed. Key in these relations is the binding of the lead drug molecule to the receptor and the inhibitory action thereon [84]. The latter can be viewed as a dependent of the first but does not necessarily result from the same molecular structure. The independence is illustrated by lenvatinib and sunitinib; they inhibit VEGFR2 by binding to the ATP-binding site with their core structure. Additional binding through a nearby structure in both compounds gives them their difference in residence time without influencing the inhibition itself [85].

The resulting collection of mainly lipophilic structures now forms the backbone of the majority of the KIs. Some molecular structures and scaffolds are found throughout the current marketed collection of smKIs. Even though the drugs inhibit a wide variety of proteins, the necessary structures to do so are similar. Table 2 lists the molecular structures of the free base smKIs ordered by primary target. Bold print indicates the proven binding moieties in the smKIs that are responsible for the inhibitory effect.

The bold printed structures in Table 2 have been shown in molecular docking and *in vitro* crystallization studies to be critical in receptor binding and inhibition [22–53]. These include highly lipophilic moieties such as (substituted) phenyls, aromatic amines, biaryl constructs and heterocyclic aromatics. Using these structures as scaffolds, a great number of studies have designed new smKIs by adding different side groups

Table 1
Approved smKIs (registered trademarks) by the FDA on March 20th 2016. Appointed BCS-classes are taken from registration documents.

Compound	Tradename	BCS[a]	Bioavailability(%)	Compound	Tradename	BSC[a]	Bioavailability(%)
Imatinib	Gleevec	I	98 [23,24]	Regorafenib	Stivarga	II	[25,26]
Gefitinib	Iressa	II	60 [27,28]	Tofacitinib	Xeljanz	III	74 [11,12]
Erlotinib	Tarceva	II	60 [29,30]	Bosutinib	Bosulif	IV	[31,32]
Sorafenib	Nexavar	II/IV	[33,34]	Axitinib	Inlyta	II	58 [35,36]
Dasatinib	Sprycel	II	[37,38]	Ibrutinib	Imbruvica	II	2.9 [39,40]
Sunitinib	Sutent	IV	[41]	Afatinib	Giotrif	I/III	[42,43]
Nilotinib	Tasigna	IV	30[b] [44,45]	Dabrafenib	Tafinlar	II	95 [46,47]
Lapatinib	Tyverb	II	<25[b] [48,49]	Trametinib	Mekinist	IV	72 [50,51]
Pazopanib	Votrient	II	14–39 [52,53]	Nintedanib	Vargatef	II/IV	5 [54,55]
Ruxolitinib	Jakavi	I	>95 [9,10]	Ceritinib	Zykadia	IV	25[b] [56,57]
Crizotinib	Xalkori	IV	43 [58,59]	Alectinib	Alecensa	II/IV	37 [60]
Vemurafenib	Zelboraf	IV	[61,62]	Cobimetinib	Cotellic	I/III	46 [63,64]
Vandetanib	Caprelsa	II	[65,66]	Osimertinib	Tagrisso	III	[67,68]
Ponatinib	Iclusig	II	[69,70]	Lenvatinib	Lenvima	II/IV	[71,72]
Cabozantinib	Cometriq	II	[73,74]				

[a] BCS, Biopharmaceutical Classification System.
[b] Estimated/Based on mass balance.

Table 2
Effective moieties in molecular structures of smKI classes.

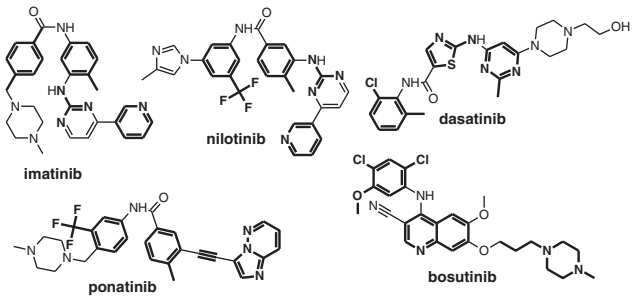
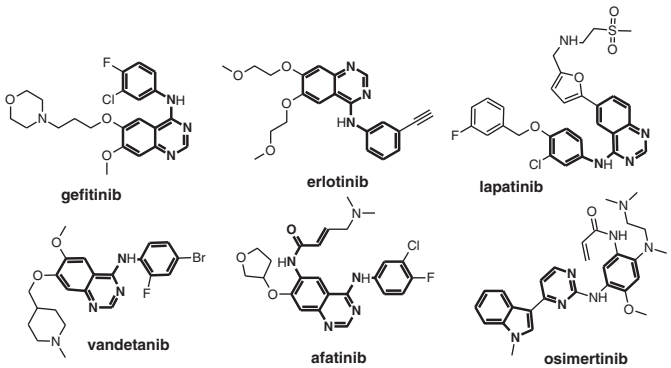
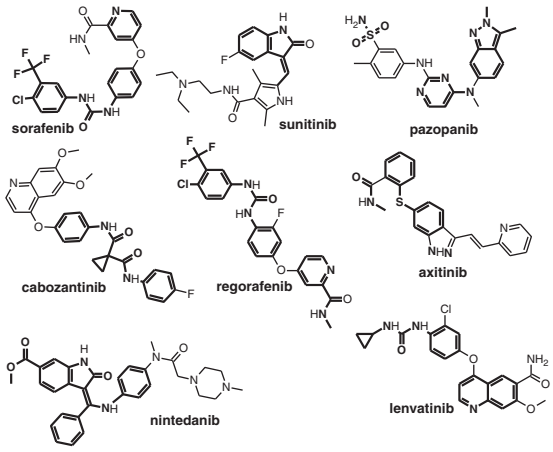
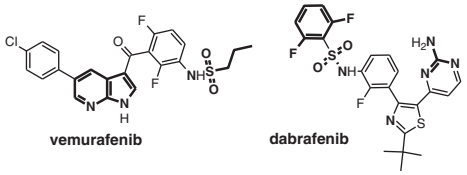
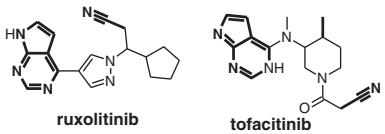
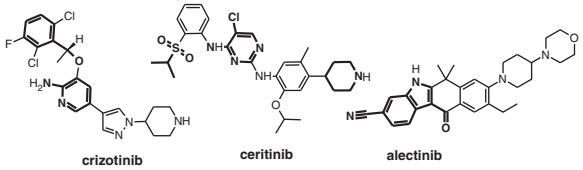
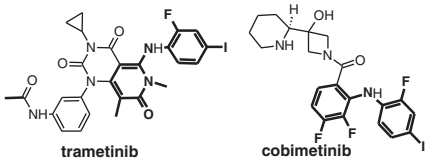
Primary target	Molecular structure(s)
BCR-Abl[a] [86–89]	
EGFR[b] [90–92]	
VEGFR[b], PDGFR[b] [85,93–102]	
B-Raf[b] [103,104]	
Jak[b] [105–108]	
ALK[b] [109–113]	
MEK[b] [114–116]	

Table 2 (*continued*)

Primary target	Molecular structure(s)
	 trametinib cobimetinib

[a] BCR-Abl, Breakpoint Cluster Region- Abelson murine lukemiaviral oncogene.
[b] EGFR, Endothelial Growth Factor Receptor; VEGFR, Vascular Endothelial Growth Factor Receptor; PDGFR, Platelet Derived Grwoth Factor Receptor; B-raf, v-raf murine sarcoma viral oncogene homolog B1; Jak, Janus Kinase; ALK, Anaplastic Lymphoma Kinase; MEK, Mitogen activated protein Kinase kinase.

[117–119]. Combining scaffolds to create a new multi-kinase-targeting smKI is also a commonly used strategy [120].

The lipophilic functional moieties and additional scaffold structures make up the larger part of the smKI molecular structure. To improve the overall aqueous solubility of a drug, drug development may include the evaluation of the possible addition of hydrophilic moieties to the core structure [121]. This addition of more hydrophilic structures may not be feasible due to the presence of hydrophobic residues that are essential for binding areas of the inhibitors however [122–125]. Adjustments to the KI chemical structures to improve the biopharmaceutical behavior can therefore only go so far. This has led to a continuous search for a delicate balance between pharmaceutical and pharmacological properties, most often resulting in the favor of the latter. As a consequence, the aqueous solubility of the free base smKI remains generally low. A recent study shows that this balance may not always lean towards poor solubility and that a combination of high inhibitor activity and hydrophilicity can be achieved for some KI structures [126].

Additionally, enhancing aqueous solubility can be achieved by constructing a pro-drug from the drug substance. Here, a solubility-improving side group is attached to the active drug, which is later removed by some form of metabolism *in vivo* after absorption [127]. Although this has not been used in the marketed smKIs, it is currently being examined for smKIs [128].

3.2. Solubility

The aqueous solubility of the smKIs is strongly influenced by environmental factors, as described in the following paragraphs. Additionally, the time points of solubility measurements determine whether an equilibrium or a dynamic value is assessed, which may differ significantly [51]. A single value can therefore not be appointed to the aqueous solubility. Reported values should be evaluated carefully, as the circumstances under which it was measured may not be adequately described.

3.3. pH-dependent solubility

The majority of the smKI scaffolds consists of nitrogen-based heterocyclic systems. An important consequence of the nitrogen-containing core inhibitory structures in combination with secondary amine moieties is an overall pH-dependent aqueous solubility.

The majority of the pK_a values of the ionizable nitrogen structures are sufficiently low to qualify them as relatively weak bases [129,130]. Table 3 lists the currently known values. The higher pK_a values commonly concern nitrogen groups that become neutral when protonated, whilst the lower pK_a values correspond to groups that attain a positive charge by protonation. For most compounds this means a relative high solubility in acidic media and a harshly reduced solubility in more alkaline environments [131–133]. Vemurafenib, Regorafenib and Trametinib are exceptions herein with an almost pH-independent solubility. This is due to their pK_a values that are either above or below the physiological pH-range.

3.4. Salt and free base polymorphs

The presence of ionizable groups in most of the smKI drug structure made the conversion to salts feasible [134]. The commercial formulations of many smKIs contain a salt in a designated stable polymorph form (Table 3). This led to a dramatic increase in solubility for some compounds, *e.g.* Imatinib, Tofacitinib and Afatinib, of which the free base forms are very poorly soluble (BCS II or IV). Their respective mesylate, citrate and dimaleate salts upgraded them to BCS-I or III. For most of the other drugs salt formation did not significantly increase solubility and they remain BCS II or IV. The reasons for using particular salt or free base polymorphs in formulations are, however often not provided in registrations texts or patents. New salt and free base polymorphs with higher solubilities are being patented and reported in literature before and after market authorization is obtained. It seems that, at least in terms of solubility, better options were and are available. Comparisons in dissolution behavior and bioavailability between various salt forms are not yet accessible. The alternative salts may prove useful in future formulation improvements however.

3.5. Solvates

Solvates are crystalline solids that contain stoichiometric or nonstoichiometric proportions of a solvent within their crystal structure. When this solvent is water, the solvate is termed a hydrate. When no solvent or water is present, a compound is termed an anhydrate. Solvates, hydrates and solventless crystals can differ significantly in solubility [135]. Most of the smKIs are formulated as anhydrates. Data on dissolution performance of solvates and hydrates are only rarely published. Dasatinib, Nilotinib, Lapatinib and Bosutinib are present as monohydrate crystals in their respective formulations. After the approval of Sprycel® in 2006, a way to produce Dasatinib anhydrate was found and this form was shown to be 2.4 times more soluble than the monohydrate variant [136]. Trametinib is formulated as a stoichiometric DMSO-solvate. In rats this increased the bioavailability of Trametinib 30-fold compared to the unsolvated form. In aqueous environment, the dissolved Trametinib.DMSO slowly precipitates as the much less soluble unsolvated form [51].

4. Formulations

Partly as a consequence of the before-mentioned factors, the solubility of a drug salt polymorph can be described thermodynamically. The following combined equation illustrates this [137]:

$$-logX = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0 T}\right) + \frac{V\Phi}{2.303RT}(\delta_1 - \delta_2)^2 \quad (1)$$

X, dissolved molar fraction; ΔH_f, latent heat of fusion (heat absorbed during melting); R, gas constant; T, temperature; T0, melting point of solute; V, molar volume of liquid solute; Φ, volume fraction of the solvent; δ, solubility parameter (expression of cohesion between molecules).

Table 3
Reported solubilities of smKIs as pure drug substance at given pH values and their types of commercial formulation.

Compound	pK_a	pH	Solubility (mg/mL)	Dosage form	Formulation composition
Imatinib mesylate	X	≤5.5	>1.6[m] [24]	T/C	Patent expired
Gefitinib FB[a]	5.4; 7.2 [28]	1.0; 7.0	21[m]; <0.001 [28]	T	L, MC, CS, P, SLS, MS
Erlotinib hydrochloride	5.4 [155]	2.0	0.4[m] [155]	T	L, MC, SSG, SLS, MS
Sorafenib tosylate	X	1.0; 4.5	0.034[m]; 0.013 [33]	T	MC, CS, H, SLS, MS
Dasatinib FB·H_2O	3.1; 6.8; 10.8 [156]	2.6; 6.0	18.4[m]; 0.008 [37]	T	L, MC, CS, HPC, MS
Sunitinib malate	9.0 [41]	1.2–6.8	>25[m] [41]	C	MN, P, CS, MS
Nilotinib hydrochloride.H_2O	2.1; 5.4 [157]	1.0; 4.5	0.28[m]; <0.1 [45]	C	L, CP, PX, SC, MS
Lapatinib ditosilate.H_2O	5; 7.2 [158]	1.0; w	10^{-6}; 0.007[m] [49,159]	T	MC, P, SSG, MS
Pazopanib hydrochloride	2.1; 6.4; 10.2 [160]	1.1	0.65[m] [160]	T	MC, P, SSG, MS
Ruxolitinib phosphate	4.3; 11.8 [161]	w	X (highly soluble) [161]	T	L, MC, SSG, MS, SC, HPC, P
Crizotinib FB	5.6; 9.4 [59]	1.6; 8.2	>10[m]; <0.1 [162]	C	MC, SC, CHP, SSG, MS
Vandetanib FB	5.2; 9.4 [147]	6.8; w	0.35[m]; 0.008 [65,147]	T	MC, DCP, CP, P, MS
Ponatinib hydrochloride	2.8; 7.8 [70]	1.7; 7.5	7.8[m]; $0.16 * 10^{-3}$ [70]	T	L, MC, SSG, SC, MS
Cabozantinib malate	X	2; >3	0.11[m]; x (very low) [163]	C	CS, SSG, SC, SA, MC
Tofacitinib citrate	5.1 [164]	1.0; w	>28[m]; 2.9 [164]	T	MC, L, CS, MS
Bosutinib FB·H_2O	7.9 [32]	<5.0; >5.0	X (high); X (reduced) [32]	T	MC, CS, PX, P, MS
Axitinib FB	4.8 [36]	1.1; >6.0	1.841[m]; $0.2 * 10^{-3}$ [36]	T	MC, L, CS, MS
Ibrutinib FB	3.8 [40]	1.2; 5.5	2[m]; 0.003 [40]	C	MC, CS, MS, SLS
Afatinib dimaleate	5.0; 8.2 [165]	<6.0; >7.0	>50[m]; 0.04 [165,166]	T	L, MC, CP, SC, MS
Dabrafenib mesylate	1.5; 2.2; 6.6 [47]	1.0; 4–8	X (VSS); X (PI) [47]	C	MC, MS, SC
Trametinib FB.DMSO	0.3 [167]	1.2; 6.8	0.0004; 0.011[m] [51]	T	MC, MN, H, CS, MS, SLS, SC
Ceritinib FB	4.1; 9.7 [168]	1.0; 6.8	11[m]; $0.2 * 10^{-3}$ [57]	C	MC, HPC, SSG, MS, SC
Alectinib hydrochloride	7.1 [169]	1.0; 6.8	0.0013; 0.0279[m] [60]	C	L, HPC, SLS, MS, CMC
Cobimetinib fumarate	8.9 [170]	1.0; 6.8	48.21[m]; 0.78 [64]	T	L, MC, CS, MS
Osimertinib mesylate	4.4; 9.5 [171]	1.2; 4.5	>3; >11[m] [68]	T	MN, H, SSF
Lenvatinib mesylate	5.1 [72]	<3.0; 3–7	X (VSS); < 0.096 [71]	C	MN, MC, CC, H, TC
Vemurafenib MPB[b]	7.9; 11.1 [62]	1.0; 6.8	$<0.3 * 10^{-3}$; $0.5 * 10^{-3m}$ [62]	T	Solid solution
Regorafenib FB	X	X	X	T	Solid dispersion
Nintedanib esilate	5.6; 9.4 [172]	1.0; ≥ 6.8	5[m]; 0.011 [55]	C	Lipophilic suspension

[a] FB = Free Base.
[b] MPB = MicroPrecipitated Bulk; M = reported maximum solubility; w = in water, pH not specified; x = value not reported; () = description given; VSS, Very slightly soluble; PI, practically insoluble; T, Tablet; C, Capsule; L, lactose; MC; Microcrystalline cellulose; CS, Crosscarmellose sodium; P, Povidone; SLS, Sodium Lauryl Sulphate; MS, Magnesium stearate; SSG. Sodium starch glycolate; H, Hypromellose; HPC, hydroxypropylcellulose; MN, Mannitol; CP, Crospovidone; PX, Poloxamer 188; SC, Silica colloidalis anhydrica; CHP, Calcium hydrogen phosphate; DCP, Dibasic calcium phosphate; SA, Stearic acid; CMC, Carboxymethylcellulose calcium; SSF, Sodium stearyl fumarate; CC, calcium carbonate; TC, Talc.

Eq. (1) clearly expresses the role of solid state crystallinity in a compound's solubility through the heat of fusion and the melting point of the drugs. The heat of fusion is the heat necessary to transform a compound from its solid to its liquid state at its melting point. Both the melting point and the heat of fusion are measures of the bond strength in the drug crystal. Stronger bonds between molecules in a crystal structure will increase both parameters and subsequently lower solubility [138]. The solubility parameters in Eq. (1) denote the significance of the molecular structure and the resulting intermolecular cohesive forces in drug and solvent in the solubility end term. The parameters are descriptors of the interaction between molecules of the drug and the solvent. If such interactions are alike in the separate drug and solvent, a drug is more likely to be soluble in that particular solvent [139]. The last term in Eq. (1) is low in such a case and the resulting solubility is relatively high.

In a physiological environment, a pharmaceutical solution may be regarded as dilute with a near-to-constant temperature [140,141]. In that situation, the molar volume approaches unity and the volume fraction may be disregarded [137]. This allows for the following simplification to a qualitative equation:

$$-\log X \approx \Delta H_f \left(\frac{T_0 - T}{T_0 T}\right) + (\delta_1 - \delta_2)^2 \quad (2)$$

Eq. (2) shows that a low heat of fusion and melting point are beneficial to a compound's solubility [142,143]. Additionally, the solubility of a drug can be further increased by creating more similarity between the solubility parameters of the drug and the solvent [144,145].

4.1. 4.1. Commercial physical mixture formulations

The commercial immediate release formulations of the smKIs are almost all designed as physical mixtures. They contain a crystal solid form. Since crystallinity is a strong determinant of solubility, the heat of fusion and the melting temperature of crystal polymorphs are closely correlated with it. Although not known for all compounds, the melting points are relatively high [26,36,62,146,147]. Furthermore, the difference between the solubility parameters of the drugs and the physiological solvent is expected to be, based on structure, relatively large [148–150]. The outcome is a very poor solubility, as is presented in Table 3. The excipients present in the physical mixtures, such as polymers and surfactants, may have some influence on the composition of the physiological solvent in the direct environment of the dissolving drug. This may lower the difference in the last term of Eq. (2). In time this effect dissipates due to diffusion of both compounds and the drug will recrystallize [151]. Table 3 lists the excipients present in the commercial formulations. As far as could be assessed, most manufacturing processes entail dry or wet mixing of the formulation ingredients and optimization of the drug particle size [152]. The latter only increases dissolution speed as it does not alter the resultant solubility through any terms in Eq. (2). The accessibility of solubility data and dissolution curves is limited in literature and patents, so the effect of the formulation on the smKIs dissolution performance is largely unknown in the public domains. The proposed dissolution methods by the FDA for bioequivalence testing of smKI formulations offer clarification to some extent however [153]. The dissolution media are all more voluminous than the stomach. In many cases the pH is adjusted to highly acidic conditions. And for some drugs surfactants are added. Although these methods are designed for quality control purposes, they provide further evidence of poor drug solubility. The non-bioequivalent dissolution media are designed to enable appropriate drug solubility (>85%) for the comparison of individual drug product batches [153]. When acidification and addition of surfactants to the media are needed to achieve this, drug solubility in bioequivalent media is likely to be significantly low. The formulation of lenvatinib is an exceptional case because it was designed with special focus on its stability. Lenvatinib has the tendency to gelate

and decompose under humid and heated storage conditions, unlike the other smKIs. Calcium carbonate and mannitol were chosen as filler/disintegrant and diluent to keep the overall hygroscopicity of the formulation low. This combination of the carrier and the hypromellose capsule make water uptake by the formulation unlikely and thus prevents gelation and hydrolytic degradation, both of which are detrimental to the bioavailability [71,154]. This capsule, which is additionally kept in a protective blister, can be stored at room temperature and humidity [71].

4.2. Alternative formulations

Changing the solid state of the drug may radically alter the first term in Eq. (2). When a move is made from the highly structured crystal form to the less rigid amorphous form the solubility can increase. This is due to the fact that amorphous materials have a melting range instead of a melting point and lack a definite heat of fusion [173]. Amorphous forms of drugs may be prepared in various ways by incorporating them in a polymer matrix in order to retain their amorphous state [174,175]. Such a system is termed a solid dispersion [176]. The commercial formulations of Vemurafenib and Regorafenib (4.2.1. and 4.2.2.) are designed like this. Additional advantages of a solid dispersion are particle size reduction, increased wettability, reduced aggregation and agglomeration and a decrease in the difference in solubility parameters through the polymer changing the physiological solvent. All these factors combined may increase the solubility long enough to improve drug absorption.

During clinical studies of three smKIs it became apparent that a simple physical mixture did not suffice in creating an adequate plasma level. These cases are discussed below.

4.2.1. Vemurafenib

Crystalline free base vemurafenib is known to exist in several polymorphs and solvates [61,62]. The most thermodynamically stable form II is practically insoluble in water with pH-values ranging from 1.1 to 9. The first clinical study with Vemurafenib was performed with the more soluble crystalline form I in a micronized capsule formulation. Form I transformed to form II over time and the observed bioavailability was low [61,62]. Shah et al. describes the development of the amorphous Vemurafenib formulation that is now used in the marketed Zelboraf® [177]. The amorphous solid dispersion was prepared by a solvent-controlled coprecipitation process as a so-called microprecipitated bulk powder. The amorphous Vemurafenib is herein stabilized by a hypromellose acetate succinate matrix to prevent crystallization [178]. Compared to the crystalline formulation, the solid dispersion demonstrated a significantly improved solubility and a five-fold increase in exposure.

4.2.2. Regorafenib

Regorafenib as a monohydrate salt is poorly soluble in water at <0.1 mg/mL [179]. The possible consequences of the poor solubility for the bioavailability were recognized early on in the formulation development. Therefore, a series of physical mixtures and solid dispersions were tested. A solid dispersion of Regorafenib in PVP 25 with a composition of 1:4 was chosen after *in vitro* dissolution screening and the assessment of rat pharmacokinetics [180].

4.2.3. Nintedanib

The drug compound Nintedanib esilate is suspended in an oily base in its commercial formulation. Nintedanib is suspended in a mixture of medium-chain triglycerides (carrier) and hard fat (thickener) [181,182]. A patent from 2009 describes the development of the formulation [183]. It stated that hydrolytic degradation seems to be problematic for the compound. In combination with the high drug load, a lipophilic carrier suspension in a hydrophilic capsule was deemed appropriate. The formulation had a higher bioavailability than the tested hydrophilic and lipophilic-surfactant systems in rats.

5. New formulations in literature and patents

Patents and exclusivities are still covering all of the smKIs, except for Imatinib [184,185]. While registered and approved alternative formulations are a long way off, there is a limited body of research published and patented at the time of writing. This section will briefly discuss the most frequently reported and patented oral formulation types.

5.1. Solid dispersions

Producing and characterizing the amorphous form of the smKIs is described throughout the patent body. Using that amorphous form in a pharmaceutical formulation is less frequently reported. This can be due to a too unstable amorphous form, a non-superior solubility or simply because the terrain is still unexplored. Xspray microparticles is one of the very few that give a description of the effect of amorphization on the dissolution of some smKIs [186]. The inventors use supercritical fluid precipitation to produce solid dispersions of Axitinib, Crizotinib, Dasatinib, Erlotinib, Gefitinib, Lapatinib, Nilotinib, Pazopanib, Sorafenib and Vemurafenib with different polymers. The patent presents a significant solubilization of the investigated compounds by the incorporation into polymeric matrices. Godugu et al. describe a spray dried solid dispersion of Gefitinib that yields a 9-fold increase in rat AUC compared to free base Gefitinib [187]. The group of Truong found that a spray dried formulation of amorphous Sorafenib, a graft polymer and SLS increased the AUC by 1.8-fold in rats [188]. Nanologica patented a nanoporous formulation with loaded amorphous Dasatinib [189]. They report no dissolution data, but state that more Dasatinib is released in Simulated Intestinal Fluid from their formulation than form crystalline drug. Song et al. prepared various solid dispersion of Lapatinib and showed an increased solubility of the products in water with 0.2% SDS [190]. Unsolvated Trametinib in a spray dried formulation had better dissolution characteristics than the commercial formulation, as patented by Ratiopharm GmBH [191].

5.2. Crystalline stabilization

A small number of patents describe improved dissolution characteristics for set of smKIs by using excipients that stabilize crystalline polymorphs as solids or as solutes. Stabilization of an unstable, more soluble polymorph of Erlotinib hydrochloride with a hydrophilic polymer can lead to better dissolution profiles. This was shown by Synthon BV [192]. Liu et al. found that the solubility of Sorafenib can be markedly increased by formulating it with Polyvinylpyrrolidone vinyl acetate copolymer (PVP-VA). The drug-polymer interaction in solution provides a supersaturated state that nearly doubles the AUC in beagle dogs [193]. The development of sustained release dosage forms of the relatively soluble Tofacitinib citrate was carried out by Pfizer [194]. This may well be an example of the development route of smKIs once the solubility issues are under control.

5.3. Cocrystals

A cocrystal is defined as a homogenous crystalline material that is made up of two or more molecules in definite stoichiometric amounts held together by non-covalent forces [195]. The physicochemistry of the so-called non-covalent derivative may be very different from a drug salt form that is held together by ionic forces [196]. A patent filed in 2015 showed an increase in solubility of Gefitinib in cocrystalline form with certain carboxylic acids [197]. Basf Se prepared several cocrystals of Dasatinib and showed that especially the combination with methyl gallate increased the aqueous solubility to 42 μg/mL from 0.36 μg/mL of the dasatinib free base monohydrate [198]. The same

was done for Nilotinib, which showed that the cocrystal with maleic acid had an almost 6-fold increase in solubility compared to the hydrochloride form [199]. Neither of the two are backed up with bioavailability data. Cocrystalline forms also improve dissolution of Lapatinib. Fabbrica Italiana Sintetici shows that a cocrystal of Lapatinib with Adipic acid has a higher solubility than Lapatinib ditosylate. In rats, however, this did not lead to an improvement of the bioavailability [200].

6. Discussion

The currently approved smKIs have important places in clinical practice for registered indications. A large fraction of these compounds is under investigation for additional indications. The new and upcoming smKIs target many of the same kinases and are designed in a similar fashion as the already marketed ones. Their general physicochemical properties might not differ significantly from those of the older smKIs. A low and variable bioavailability is an enormous problem and may also lead to additional expenses in the patient treatment. High drug loading may be necessary to reach certain plasma levels for drugs with a low bioavailability with due consequences. The narrow therapeutic window of the drugs reflect in serious side effects and reduced activity above and below certain plasma concentration thresholds, respectively [17,201]. A variable bioavailability therefore often requires plasma levels to be monitored over a given time as part of a therapeutic drug monitoring (TDM) regimen which in part takes the advantages of oral therapy away. This is illustrated by the necessity of dose adjustments of smKIs in 25% of the patients treated with these drugs in our own institute.

Poor solubility may also pose a problem for smKIs that do not bind to the active site of the kinase that they inhibit. Such smKIs can bind to a regulatory site of a kinase, *e.g.* Rebastinib. The molecular structure of Rebastinib contains similar groups as the presented smKIs in Table 2, which are necessary for binding [202]. Solubility data of this drug is not yet available in the public domain. However, based on its structure, rebastinib is expected to be poorly soluble.

Plain and relatively uncomplicated formulations may be troublesome and can have very costly consequences during early clinical development. The first clinical trial with vemurafenib is exemplary. During this trial, it was discovered that the formulated crystal polymorph exhibited a low bioavailability. A new formulation with amorphous vemurafenib was produced and the clinical trials had to be repeated [61]. Although such a case is probably an exception, it is worth noticing that this might have been prevented.

With the incidence of cancer on the rise and the value of smKI therapy thoroughly established, the challenges of further improving the therapy are gaining value [203]. With a disease that has such significant consequences for patients, therapeutic uncertainties are all the more undesired. Predicting and addressing these uncertainties, preferably in an early stage of development, seems more than appropriate. Simple and straightforward formulations are surely preferred in terms of cost effectiveness of development and ease-of-production. The experience with the smKI group teaches the most valued lesson that overall cost effectiveness and the ease-of-treatment may not at all be benefitted by such choices however. Speed and efficiency are becoming characteristics of drug development [204]. The future challenges will therefore lie in the implementation of thorough screening of formulations and dosage forms into the overall drug development process. To ensure efficiency, a useful translation from *in vitro* dissolution data to the *in vivo* setting is needed. As *in vitro-in vivo* predictability from simple dissolution setups is often troublesome, the adoption of methods such as the gastrointestinal model TIM may prove to be valuable [205].

The solubility-induced variable bioavailability and the accompanying risks and costs may largely benefit from formulations with improved performance. While most patents and exclusivities are still pending and new or bioequivalent formulations are not yet eligible for approval, formulation research increasingly highlights the opportunities for improved drug forms of approved and to-be-approved smKIs.

7. Conclusions

Due to the very distinct targeting of the smKIs, biocompatible physicochemistry is driven to the edge. This places a strain upon bioavailability and presents challenges to formulation scientists.

'Classical' physical mixtures may work to achieve a relatively high bioavailability for some compounds, namely Imatinib, Ruxolitinib and Dabrafenib. This is certainly not the case for the majority of smKIs however. Bearing patents and exclusivities in mind, the past experiences can lead to new and innovative formulations that may provide further improvement of the efficacy of anti cancer treatment.

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