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PERSPECTIVE

High-Tech Drugs in Creaky Formulations

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ABSTRACT Recent literature reviews and registration documents covering novel Signal Transduction Inhibitors in the treatment of cancer paint a picture of inefficiency and variability, where formulation improvements could be valuable. In this article, we discuss apparent drug design flaws as we impose the current standard formulation practice.

KEY WORDS anticancer drugs · biopharmaceutics · formulation · pharmaceutics

ABBREVIATIONS

BCS	Biopharmaceutical classification system
GI	Gastro-intestinal
STI	Signal transduction inhibitor

Combining personalized chemotherapy with oral drug ingestion has demonstrated to be an almost golden duo. The success of this combination has been illustrated by the registration of 28 oral signal transduction inhibitors (STIs) in the past years. This group of therapeutics has proven its value in the clinic and a large number of the member drugs have become the standard care for an increasing amount of tumor types. Despite the efficient and specific nature of the drugs, the full potential of this inhibitor class has yet to be realized. In harsh contrast to the pharmacological fine tuning done for this group stands the nascent development of their pharmaceutical formulations. At least 16 of these highly specific drugs, with sometimes life lengthening properties, suffer from low bioavailability and high variability, which in many cases could be improved with more optimal formulations (1).

Recent analyses of the pharmacokinetic properties of STI formulations present a troubling picture. As defining properties, we are confronted with low, fluctuating and highly susceptible exposures due to restricting absorption and/or first pass clearance (2,3). The results of these studies expose a situation where an apparent imbalance exists between the development of the drug substance and that of the formulation. Biopharmaceutical issues and considerations are seemingly not prioritized by drug innovators where absorption is a limiting factor. As a large majority of STIs are classified as either unfavorable Biopharmaceutical Classification System (BCS) class II or IV (further explained and presented in Fig. 1), additional attention to formulation design was especially warranted here.

Inevitably, this leads to situations where some drugs are being wasteful. Firstly, in the most literal sense, since large parts of the drug substances are not absorbed into the systemic circulation. These parts are subsequently discarded. An exemplary case is pazopanib of which only 21% is absorbed into the systemic circulation (1). Secondly, further consideration of the pricing of personalized chemotherapy makes these matters even more deplorable. In the dire patient's experience of cancer, every additional uncertainty is one too many and inadequate medication forms should not be added to this. Most worrying of all, is the imaginable loss of life quantity and quality that patients might suffer due to insufficient drug efficacy over time.

The variability in exposure has drawbacks that stretch beyond the obvious impact on drug efficacy and possible toxicity. In order to avoid as much (intrapatient) variability as possible, patients are requested to combine or avoid intake with food and certain comedication. To restrain the interpatient variability, patients are subjected to therapeutic drug

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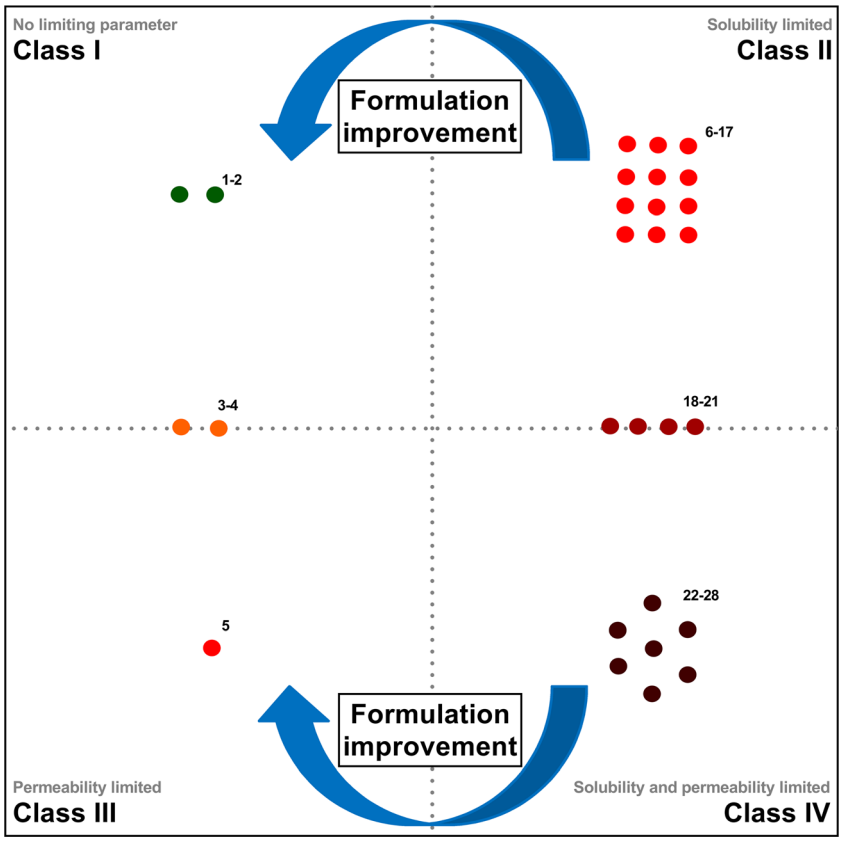

Fig. 1 Currently marketed STIs in their respective BCS-class. Class 1, drugs with good solubility and permeability; Class II, drugs with poor solubility and good permeability; Class III, drugs with good solubility and poor permeability; Class IV, drugs with both poor solubility and permeability. 1–2, Imatinib, Ruxolitinib; 3–4, Afatinib, Cobimetinib; 5, Osimertinib; 6–17, Erlotinib, Gefitinib, Dasatinib, Lapatinib, Pazopanib, Vandetanib, Ponatinib, Cabozantinib, Regorafenib, Axitinib, Ibrutinib, Dabrafenib; 18–21, Sorafenib, Nintedanib, Alectinib, Lenvatinib; 22–28, Sunitinib, Nilotinib, Crizotinib, Vemurafenib, Bosutinib, Trametinib, Ceritinib. (1,9) Changing the formulation of a class II or IV compound may shift its absorption behavior towards class I and III, respectively.

monitoring with increasing frequency (4). In fact, in our institute dose corrections are warranted in 25% of the cases for patients treated with STIs due to inadequate exposure. This current practice entails a costly, high maintenance therapy.

The fact that at least 50% of the STI formulations are presently performing below what is reasonably achievable is further highlighted by the effect that food and comedication can have on drug exposure (1,5). Ingesting food concomitantly with an STI generally can have a profound effect on the exposure of that drug (1,3). A clear example of effect is the significant increase in exposure up to 4.7-fold of pazopanib, vemurafenib and lapatinib when they are taken with food (6). Such effects reveal solubility alterations in different environments and are often good indicators of the poor performance of the pharmaceutical formulation. The same is true for pH effects; acidification of the GI-tract has been shown to lead to additional exposure to Erlotinib, whilst acid-reducing drugs can sharply lower the bioavailability of a large group of STIs (1,7).

Therapeutic specificity is this drug class' greatest asset. The molecular structures are tailor made and well balanced out to bind and inhibit the proteins that have gone haywire in various tumor types.

Yet these structures also turn out to be complicating factors that should be recognized and taken into account when developing STI formulations. Appropriate binding and inhibiting moieties often contain relatively lipophilic structures that make pure drug dissolution increasingly difficult. This is especially true for the STI group. Data from pharmacokinetic studies show a strong correlation between drug solubility, bioavailability and pharmacokinetic variability thereof (8). This combination of facts should have sparked ample response in formulative development. For the STIs, at least, the efforts and attempts at improving biopharmaceutical properties are only marginally available.

In the present collection of STI drugs appropriate effort put into the formulations has actually led to drastic solubility and bioavailability improvement. The solubility of five compounds (Imatinib, Ruxolitinib, Dabrafenib, Cobimetinib and Osimertinib) was accommodated by the selection of a relatively soluble salt form (9). A statement could be made in favor of formulating these drugs as tablets or capsules from simple powder mixtures. Yet for the vast remaining majority this is certainly not the case. Contrary to the desirability of an intricate formulation test cycle, all but three drugs are marketed as physical mixtures. Perhaps the most infamous of the three is Vemurafenib. Vemurafenib's first clinical trial formulation was swiftly altered to Micro Precipitated Bulk which increased the solubility 30-fold, but only after the previous Phase I trial revealed a very poor bioavailability due to solubility issues. This belated solubility-improving alteration in the formulation also increased patient exposure by a 5-fold (10). This

alteration is a typical case study that can be added to the before mentioned wasteful state of affairs.

An increasing number of studies illuminate an array of methods that can improve drug solubility and subsequently show a related boost in exposure. Techniques that produce solid dispersions, cocrystals and nanoformulations have all proven to be beneficial for STIs. Even simple changes, such as a change in excipient composition, can result in a better performance (11). Inclusion of such techniques into early drug development stages may prove to be valuable ventures and lead to more efficient drug formulations.

The rate of drug discovery and development has sped up in the past years. Along with accelerated authority registration it has brought new therapeutic options to patient faster than ever before. It seems, however, as if the hastened pace of personalized cancer drug development has a dubious side as well. In this field where time is of the essence, simple and time-saving formulation development is favored. These formulations are designed to roughly deliver the drug exposure that is needed for a therapeutic effect, albeit with large deviations. Through the recent decades we have learned that a development course like this may save the pharmaceutical industry from certain effort and costs. In reality, however, the efforts and costs are merely postponed until they are left to be dealt with by clinicians and eventually, the patients.

The realization that the virtue of cancer therapy is not just the sum, but the product of all the actions and decisions taken from drug discovery to patient guidance, is eminent in this matter. Hence, it follows that the drug manufacturers play a significant role therein. Drug manufacturers should hold themselves to a self-explanatory intrinsic ethical commitment to optimize a drug's mode of administration. When such a commitment is well organized in an early stage of development, commercial and financial interests are unlikely to be compromised.

With the incidence of cancer still on the rise and the molecular exploration of its causes still ongoing, it is very likely that more STIs are to appear in the foreseeable future. As long as the largest portion of cancer care's weight is still pulled by chemotherapy and the shift towards personalized drugs continues, the issue of drug performance will remain a crucial one. To ensure a future where cancer drugs approach optimal capability, in both financial and therapeutic sense, the pharmaceutical field must increase investments in chemotherapy formulation.

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