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Review Article

Comprehensive Review Of Pazopanib With Low Oral Efficacy And Bioavailability

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ABSTRACT

Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) that is taken orally with an indication for advanced renal cell carcinoma (RCC) and advanced soft tissue sarcoma (STS). Pazopanib is an inhibitor of c-KIT, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β) and vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3) that help block tumor angiogenesis and proliferation. While it has shown important clinical activity in some tumors, its activity could be restrained by its limited and variable oral bioavailability. Pazopanib belongs to Biopharmaceutics Classification System (BCS) Class II which is defined as having low aqueous solubility and high membrane permeability. It is highly pH-dependent so the amount that dissolves and is absorbed through the gastrointestinal tract can vary with the pH in the stomach. Additionally, systemic exposure to the drug is highly variable between patients due to factors such as food intake, gastric acid-suppressing therapy, extensive plasma protein binding and hepatic metabolism. These parameters may impact the efficacy of treatment and can make it challenging to optimize treatment. Pharmaceutical researchers have been targeting barriers such as these in recent years, in an effort to develop more sophisticated formulations strategies. Drug delivery systems and approaches such as solid dispersions, lipid drug delivery systems, self-emulsifying drug delivery systems, nanocrystals, polymeric nanoparticles, cyclodextrin inclusion complexes, and amorphous drug formulations have proven to be promising during preclinical and clinical trials to enhance the solubility and oral absorption of drugs. In this review, we summarized the physicochemical properties, pharmacokinetic profile, causes of poor oral bioavailability, clinical relevance of pharmacokinetic variability, and existing formulation strategies to improve the efficacy of pazopanib. Emerging technologies and potential future directions for reducing variation in clinical

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outcomes through oral drug delivery are also discussed.

INTRODUCTION

Remarkable progress in early diagnosis, targeted therapy, immunotherapy, and precision medicine has not prevented cancer from remaining one of the leading causes of death worldwide. In recent two decades, a number of molecular inhibitors have been developed to specifically inhibit molecular pathways contributing to the growth and neo-angiogenesis of diverse malignancies and revolutionized their management. In this group, tyrosine kinase inhibitors (TKIs) have become important and indispensable drugs in today's cancer therapy, as they are known to affect intracellular signaling pathways essential to cancer progression without causing toxic side effects as commonly seen with conventional cytotoxic chemotherapy.

Pazopanib is an orally available multi-targeted tyrosine kinase inhibitor developed to inhibit tumor angiogenesis through simultaneous blockade of multiple receptor tyrosine kinases, an effect that differentiates it from the first generation of oral multi-targeted tyrosine kinase inhibitors. In 2009, FDA approved it for advanced renal cell carcinoma and was later approved for use in soft tissue sarcomas because of promising clinical results. In addition, pazopanib inhibits c-KIT, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), fibroblast growth factor receptors to some degree and vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3) and blocks the growth of new blood vessels in tumor tissue and the growth of cells.

Pazopanib offers a number of clinical benefits over conventional chemotherapeutic drugs. It is taken by mouth and provides selective molecular targeting and has shown to be effective at slowing the course of disease in multiple solid tumors. Its favorable pharmacodynamic profile is offset, however, by its suboptimal pharmacokinetic properties. However, pazopanib treatment is limited by the drug's low and variable oral bioavailability. Drug uptake is very variable in patients, resulting in wide inter-patient fluctuations in plasma drug levels and variability in therapeutic response.

The oral route remains the preferred route of drug delivery because of its convenience, good patient compliance, lower healthcare costs, and suitability for long-term therapy. However, drugs administered orally must dissolve rapidly in gastrointestinal fluids and be efficiently absorbed through the intestinal epithelium. This is a real problem in the case of Pazopanib due to its highly low water solubility and intensive dependence on acidic gastric conditions for dissolution.

Based on the Biopharmaceutics Classification System (BCS) pazopanib is classified as Class II drugs, characterized by high intestinal permeability and low aqueous solubility. In these circumstances, the rate of dissolution of a drug becomes the rate-determining step that regulates systemic absorption of the drug. Pazopanib has very poor solubility at neutral pH. When it reaches the more alkaline environment of the small intestine, the dissolved drug rapidly precipitates, reducing its absorption. About this time, only a portion of the amount given reaches the systemic circulation. The exposure to pazopanib is also variable by several other factors. Drug dissolution is significantly lower with the use of a gastric acid suppressant (proton pump inhibitor & histamine-2 receptor antagonists) due to their effect of raising

pH in the stomach. Similarly, the presence of food in the intestinal tract can greatly modify the absorption of a drug and result in greater systemic exposure than if taken on an empty stomach. Food effects add an additional level of variation and

result in clinical recommendations to take pazopanib on an empty stomach. Systemic exposure and potential drug–drug interactions are also influenced by extensive CYP3A4-mediated metabolism and very high plasma protein binding (>99%).

Reduced absorption of drugs is not the only clinical consequence for poor oral bioavailability. Plasma drug levels can vary greatly from one patient to another who takes the same dose. However, inadequate drug exposure may reduce tumor response, whereas excessive drug exposure may increase the risk of adverse effects, whilst radiation exposure above the recommended dose will lead to a higher probability of side effects such as hypertension, hepatotoxicity, diarrhea, fatigue and hand-foot syndrome. This pharmacokinetic variability imposes a challenge to optimize dosing and raises the interest of TDM to customize pazopanib therapy to the patient's needs. In response to these concerns, scientists have been actively developing drug delivery systems to enhance pazopanib's ability to deliver orally. Several formulation approaches have been explored such as Amorphous Solid Dispersions, Self Emulsifying Drug Delivery Systems, Lipid-based Formulation, Polymeric Nanoparticles, Nanocrystals, Cyclodextrin Inclusion Complex, Mesoporous Silica Carriers, Hybrid Nanocarriers. The goal of these technologies is to improve the aqueous solubility, dissolution rate, intestinal absorption and systemic exposure to reduce variability and without loss of safety and stability. Beyond typical formulation strategies, new techniques like 3D printing, pH dependent nanoparticles, polymeric micelles, and AI-driven formulation optimization are opening the door to novel formulations to enhance the clinical behavior of poorly soluble agents for the treatment of cancer. Ultimately, integrating pharmaceutical nanotechnology with personalized medicine may enable individualized pazopanib therapy with improved clinical outcomes.

This review aims to give an overview of pazopanib including a detailed discussion of factors which contribute to its low oral efficacy and bioavailability. This review discusses the physicochemical properties that influence oral drug absorption, the pharmacokinetics of these drugs, the significance of the pharmacokinetics variability in the clinic, the formulation strategies that have been devised to tackle these limits, and the future outlook on the improvement of oral drug delivery. This review presents key developments of drug design and clinical studies and synthesizes them to gain a deeper understanding of one of the most significant challenges with pazopanib treatment.

2. Chemical Structure, Physicochemical Properties, Mechanism of Action, and Pharmacological Profile

2.1 Chemical Structure of Pazopanib

Pazopanib is a small molecule, oral, multi-targeted tyrosine kinase inhibitor (MTKI) of the aminopyrimidine-type. It is sold under the name “pazopanib hydrochloride” which has enhanced handling and formulation of the active pharmaceutical ingredient. The molecular formula for the free base of the drug is $C_{21}H_{23}N_7O_2S$ and it has a molecular mass of around 437.5 g/mol.

It has a molecular structure that includes aromatic rings amongst its building blocks, as well as some nitrogen atoms in the form of heterocyclic compounds, and sulfur groups which provide the molecule with enhanced selective binding to receptor tyrosine kinases. The structural characteristics of these molecules lead to their high affinity to ATP-binding pockets of several receptor kinases that play role in tumor

angiogenesis. They are also involved in making this molecule very lipophilic and poorly soluble in water, which is particularly challenging for oral formulation.

Pazopanib crystallizes further reducing its gastrointestinal tract dissolution. The more highly ordered the crystalline structure, the more energy is required to dissolve the drug. As a result, oral bioavailability is low, with only a portion of the pazopanib that is consumed being present for absorption in gastrointestinal fluids.

2.2 Physicochemical Properties

The main physicochemical properties directly affect the absorption, distribution and overall therapeutic efficacy of pazopanib. Several of these properties are responsible for the fact that the drug is highly membrane permeable but has low oral bioavailability.

Table 1. Important Physicochemical Properties of Pazopanib

Property	Description
Molecular formula	$C_{21}H_{23}N_7O_2S$
Molecular weight	~437.5 g/mol
Dosage form	Oral tablets
BCS classification	Class II
Solubility in water (physiological pH)	Very low in water at physiological pH
Lipophilicity	High (Log P approximately 3–4)
Protein binding	>99%
Primary metabolism	CYP3A4
Elimination half-life	Approximately 30 hours

Among these characteristics, poor aqueous solubility represents the greatest obstacle to efficient oral absorption.

2.3 Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) classifies orally administered drugs based on their aqueous solubility and intestinal permeability.

Pazopanib falls into the BCS Class II category.

Class II compounds have:

1. Low aqueous solubility
2. High intestinal permeability

For these drugs, dissolution in gastrointestinal fluids—not intestinal permeability—is the rate-limiting step for absorption. While a dissolved pazopanib penetrates readily into the cells of any membrane, the small amount of pazopanib administered as suspension only dissolves in the gastrointestinal fluids. Hence dissolution is the primary determinant of oral absorption, thus making it more if it can be improved. This property is why the majority of the formulation research with pazopanib focused on enhancing aqueous solubility, instead of making changes to membrane permeability.

2.4 Solubility Characteristics

Pazopanib exhibits extremely poor aqueous solubility, one of its major physicochemical

limitations. The drug is a weakly basic compound that is very sensitive to pH of its environment. Under the acidic conditions of the stomach, protonation increases the solubility of pazopanib. The pH of the intestinal contents, however, increases significantly after the gastric emptying and precipitation of the dissolved molecules in the intestinal tract is rapid.

This precipitation causes a huge reduction in the concentration gradient that is required for passive diffusion through the intestinal epithelium. Thus, the bioavailability of pazopanib is low after oral administration.

It has been established that dissolution decreases significantly at pH values above approximately 4. This phenomenon is the reason why patients on proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) have lower drug exposure.

2.5 Lipophilicity

Pazopanib has relatively high lipophilicity. The lipophilic drugs, are typically efficient membrane permeable drugs, which cross the membranes easily due to the fact that drugs can pass through the phospholipid bilayers. But large lipophilicity tends to decrease the aqueous solubility. Thus, pazopanib is a general example of the drug paradox in which better permeability across the membranes is balanced by bad dissolution. This property of lipid solubility versus solubility is among one of the major challenges of many contemporary TKIs in drug formulation.

2.6 pH-Dependent Dissolution

Pazopanib, in contrast to many traditional oral products with good gastrointestinal (GI) tract dissolution, has significant pH-dependent dissolution. The drug dissolves relatively well in the acidic environment of the stomach.

Following gastric emptying:

1. intestinal pH increases,
2. dissolved drug precipitates,
3. dissolution rate declines,
4. absorption becomes incomplete.

Precipitation depends on the degree of gastric emptying, intestinal pH, food intake and co-administered medications. This is the reason for significant differences in the body levels seen in patients who have been given an equal oral dose.

2.6 Stability Characteristics

Pazopanib is chemically stable in recommended storage conditions. Formulation stability is important, however, when considering its physical stability. Many advanced formulations make use of the relatively rapid rate of dissolution of amorphous pazopanib, converting crystalline pazopanib into amorphous forms. Unfortunately, amorphous drugs exhibit greater thermodynamic instability and are prone to recrystallization in storage. Thus, in the formulation of novel dosage forms, formulation scientists have to sacrifice dissolution to maintain long-term physical stability.

3. Mechanism of Action

Angiogenesis plays a critical role in cancer progression. In solid tumors, the growth of their cells depends on the continual formation of new blood vessels since it is hard for blood vessels to traverse distances of more than a few millimeters. This process is called the process of angiogenesis and supplies oxygen and nutrients; it also allows for invasion and metastasis of tumors. There are multiple signaling pathways that control Angiogenesis, and the vascular endothelial growth

factor (VEGF) pathway is dominant. Many cancer cells can also up-regulate expression of VEGF, thus stimulating an overproduction of endothelial cells and abnormal vascular growth. Blocking these signaling pathways starves tumor cells for their blood supply and slows disease progression. Pazopanib is a dual-target inhibitor that targets multiple receptor tyrosine kinases, whereas the highly selective inhibitors inhibit only one receptor type.

It mainly acts on these target molecules:

1. VEGFR-1
2. VEGFR-2
3. VEGFR-3
4. PDGFR-α
5. PDGFR-β
6. c-KIT

Pazopanib binds competitively to these receptors at the ATP binding domain, blocking receptor phosphorylation and blocking the intracellular signaling pathway needed for the growth of tumors and for the growth of new blood vessels.

3.3 Inhibition of VEGF Signaling

Pazopanib's molecular targets include VEGFR-2 which is believed to be the most important pathway through which pazopanib is able to exert its antitumor activity. Usually activated by VEGF signaling, these intracellular pathways encourage:

1. endothelial cell proliferation,
2. migration,
3. survival,
4. vascular permeability,
5. formation of new blood vessels.

Pazopanib inhibits receptor phosphorylation and subsequent signal transduction, which helps to inhibit angiogenesis and limit tumor blood supply. Ultimately, there is a reduction in the vascularization, which restricts tumor size and progression.

3.4 Inhibition of PDGF Signaling

Platelet-derived growth factor receptors recruit and stabilize pericytes surrounding newly formed blood vessels. Pazopanib disrupts the growth of tumor-vessels and increases anti-angiogenic activity by inhibiting PDGFR signaling. Blocking VEGFR together with PDGFR has a greater anti-tumor effect than blocking either pathway alone.

3.5 Inhibition of c-KIT

The c-kit receptor is involved in the control of cellular growth and development in various tissues. Abnormal activation of c-KIT signaling is present in certain malignancies. Pazopanib inhibits this pathway, contributing to its antitumor activity in susceptible cancers.

3.6 Overall Pharmacological Effects

Inhibition of multiple receptor tyrosine kinases has various therapeutic effects:

1. suppression of tumor angiogenesis,
2. prevention of endothelial cell growth, and
3. Decrease in tumor blood vessel density,
4. decreased tumor growth,
5. delayed metastatic spread,
6. Prolonged progression-free survival in responsive cancers.

In contrast to cytotoxic chemotherapy which kills actively growing cells, pazopanib mainly works on the tumor tissue by inhibiting the growth of new blood vessels that are required for tumor growth. This means that this mechanism, in general, has less systemic toxicity than normal chemotherapy, but adverse effects including hypertension,

hepatotoxicity, diarrhea, fatigue, hypothyroidism, depigmentation of the hair and hand-foot syndrome pose a clinical risk for regular monitoring throughout treatment.

3.7 Clinical relevance of the mechanism

Pazopanib's wide spectrum of receptor inhibition activity underlies its clinical activity in advanced renal cell carcinoma and soft tissue sarcoma. However, maintaining sufficient drug levels within the body to inhibit these molecular targets is dependent upon obtaining the appropriate systemic drug levels. Sustained pharmacokinetics variation may occur in some patients, resulting in plasma concentrations that may not be optimal for therapeutic benefit; poor dissolution and/or incomplete gastrointestinal absorption may result in failure to reach the therapeutic plasma concentration in some patients. There is a growing need to enhance the oral bioavailability as it has become an important pharmaceutical goal in relation to clinical performance. The linkage of pharmacological activity and the systemic drug exposure highlight the need for advanced pharmaceutical drug delivery systems that can offer improved dissolution and steady plasma exposure to the drug. The following section discusses the pharmacokinetics of pazopanib and the factors responsible for its poor oral bioavailability, will be covered, thereby encompassing the background of which to understand current and future options for pazopanib formulation.

4. Pharmacokinetics, Oral Bioavailability and Factors that impair oral efficacy.

The pharmacological activity is only part of the formula that determines the success of an orally administered anticancer drug; being present in systemic circulation at the right time and concentration is the second part. Pazopanib has excellent vivo potency as a multi-targeted tyrosine kinase inhibitor, but there are variable and sub-optimal oral bioavailability issues that can reduce the efficacy of this drug. This variability is the result of the combination of poor physicochemical properties, gastrointestinal factors, metabolic processes and patient specific factors. Therefore, knowledge of the pharmacokinetic profile of pazopanib is crucial for elucidation of the mechanism of its clinical failures and to eliminate methods with which to enhance the oral delivery of pazopanib.

4.1 Pharmacokinetic Profile

Pazopanib is taken orally (by mouth), and it is absorbed through the small intestine. Peak plasma concentration (Tmax) 2–4 hours after administration under fasting conditions, but considerable interpatient variation has been reported. Its elimination half-life is approximately 30 hours, allowing once-daily dosing in most patients. After absorption, pazopanib distributes widely throughout the body with >99% plasma protein binding (mainly to albumin and α_1-acid glycoprotein). This results in a very small percentage of drug being free, or unbound, and so able to exert a pharmacologic effect. The presence of significant protein binding will mean that the drug will remain in the blood for longer but will also mean that there may be clinically significant drug–drug interaction with other highly protein-bound drugs. Pazopanib is highly metabolized in the liver; the major metabolic enzyme is cytochrome P450 3A4 (CYP3A4). Minor contributions from CYP1A2 and CYP2C8 have been identified, as well. The metabolites produced tend to have low pharmacological activity, generally much reduced when compared to the parent compound. The elimination route is mainly

via faeces and only trace amounts appear via urine. While these properties of the drug seem to be very favorable, the bioavailable fraction of orally administered drug is very variable due to incomplete dissolution during absorption in the gastrointestinal tract. As a result, the plasma levels of patients given the same dose orally can vary widely.

4.2 Oral Bioavailability of Pazopanib

Oral bioavailability is the fraction of an orally administered dose that reaches the systemic circulation unchanged. Many medications which are given orally have high bioavailability leading to predictable effects and simple dose optimization. In contrast to pazopanib, however, there is only limited and highly variable oral bioavailability of pazopanib, which makes it challenging to achieve stable systemic exposure of pazopanib in a variety of patient cohorts. Once dissolved, pazopanib readily permeates biological membranes; however, its poor dissolution limits absorption. The problem is that not all the dosage form that's administered can dissolve in gastrointestinal fluid as it passes to the absorption site. Thus, for orally absorbable drugs, the rate at which the drug is dissolved becomes the limiting step in the transport of the drug through the membrane.

Systemic exposure to pazopanib measured in clinical pharmacokinetic studies has been shown to be very variable between patients receiving identical doses of pazopanib. These variations are due to a number of factors, such as variability in gastric acidity, gastrointestinal physiology, concurrent medications, dietary intake, liver function, and genetic variations in drug metabolism. This variability makes treatment more difficult as under- or over-exposure could have a negative effect on the outcome of therapy.

1.3 Low Aqueous Solubility: The Primary Limitation

Poor aqueous solubility is the most important factor that impedes pazopanib bioavailability when it's taken by mouth. The drug is poorly soluble in water at physiologic pH. Therefore, only a small percentage of the tablets will dissolve in the gastrointestinal fluids after taking them by mouth. Drug molecules must be dissolved before they can be absorbed across the intestinal epithelium. Additionally, pazopanib possesses a crystalline effect. The molecules of a drug are strongly bound in a crystalline lattice by intermolecular forces and need substantial energy input to break the binding forces in order to dissolve the form itself. This has led to slow dissolution, especially in the not so acidic environment of the small intestine where most of the drug absorption will take place. In general, with BCS Class II molecules like pazopanib, enhancing the aqueous solubility results in greater oral bioavailability. This principle has been exploited in the majority of formulation research to improve the dissolution without changing the permeability of the product.

4.4 Influence of Gastric pH

The highly pH-dependent solubility is one of the most remarkable properties of pazopanib. Pazopanib is a weakly basic compound, which only dissociates well in very acidic conditions. In the stomach, the pH is acidic, which results in protonation of the drug and thus an apparent increase in its solubility. After gastric emptying, intestinal pH increases, the pH in the intestine rises significantly. In such a case, the loss of the protonated form of the drug molecule is rapid and precipitates the molecule out of the solvent. This precipitation decreases the quantity of absorbed drug by the intestinal mucosa. The consequences of this phenomenon are significant for the clinical

management of the patient. Patients taking drugs that raise gastric pH often have lower systemic concentration of pazopanib. Common examples include:

1. Proton pump inhibitors
2. Histamine-2 receptor antagonists
3. Antacid preparations

These drugs increase gastric pH, thereby reducing drug dissolution. Consequently, the concomitant use of acid-suppressive therapy should be avoided wherever possible and carefully controlled the timing of administration if concomitant therapy is necessary, as recommended in the prescribing information.

4.5 Food Effect on Drug Absorption

Administration with food, particularly high-fat meals, results in higher systemic exposure than administration under fasting conditions. This rise is thought to be due to several physiological changes which occur when feeding; these are the extended gastric residence time and the increase in bile salt secretion, wetting of the drug particles, and increased solubilisation of lipophilic compounds. The food effect, which may lead to potentially high plasma concentrations may seem useful but can vary considerably between different patients. There is an increased risk of adverse effects with increased exposure such as hypertension, hepatotoxicity, gastrointestinal toxicity and fatigue. In the current clinical guidelines, pazopanib should be taken at least 1 hour before or 2 hours after a meal. A uniform dosing regimen creates more consistency in doses for systemic drug effects in different patients.

4.6 Slow Dissolution Rate

Another crucial parameter that may influence the oral efficacy of pazopanib is the rate of dissolution. Complete dissolution of the drug in the stomach before gastric emptying rarely occurs. The undissolved solids eventually pass into the small intestine, and the increased pH in the small intestine also decreases the amount of dissolution, while increasing the amount of precipitation. The Noyes–Whitney equation shows that dissolution rate is related to particle size, surface area, saturation solubility, diffusion coefficient and boundary layer thickness. The intrinsic solubility of pazopanib is low and the size of its crystals in the standard tablet dosage form is relatively large, making its dissolution in water slow. This knowledge has been the basis for various formulation approaches, which include methods to enhance the effective surface area, decrease the particle diameter and and/or keep a drug supersaturated in gastrointestinal fluids.

4.7 First-Pass Metabolism

Variability in systemic drug exposure is also mediated by liver metabolism although poor dissolution is an important barrier to absorption. After absorption pazopanib is metabolised extensively in the liver mainly by CYP3A4 mediated oxidation. Plasma concentration, therefore, can be significantly changed when combined with the use of inhibitors or inducers of CYP3A4. When it is added with strong CYP3A4 inhibitors, its systemic exposure is likely to be enhanced and may lead to toxicity. In contrast, strong CYP3A4 activators can increase drug metabolism and can lead to lower levels of the drug in the blood stream which can potentially decrease therapeutic effectiveness. The impact of metabolism on these drug interactions also adds additional challenges for optimizing doses in the oncology setting, where patients are frequently taking multiple drugs.

4.8 Interpatient Variability

A defining feature of pazopanib pharmacokinetics is substantial interpatient variability. Dose-related systemic drug exposure can be affected by the following physiological and clinical factors: The pH of the stomach and the production of acid.

1. Gastric emptying rate
2. Intestinal motility
3. Hepatic function
4. Age
5. Body composition
6. Concomitant medications
7. Variations at the genetic level that affect drug metabolism
8. Adherence to the diet instructions in the patient.

As a result, identical oral doses may produce markedly different plasma concentrations among patients. This variability contributes, in part, to variation in responses and/or side effects that have been seen in clinical practice.

4.9 Clinical Consequences of Poor Oral bioavailability

The pharmacokinetic profile has implications for the management of pazopanib patients. Insufficient systemic drug exposure may fail to adequately inhibit tumor growth. On the other hand, the more that drugs are exposed, the more likely that dose dependent side effects will occur, which may require drug breaks or dose adjustments. A cause-and-effect relationship between pazopanib plasma exposure and treatment response have been shown in clinical studies, indicating that adequate systemic exposure is associated with improved progression-free survival. Such observations have led to a growing interest in therapeutic drug monitoring (TDM) to tailor dose based on plasma levels. But the limitation of poor dissolution and gastrointestinal absorption cannot be solved by making use of pharmacokinetic monitoring completely. Therefore, optimizing the formulation of pazopanib is one of the most promising strategies for improving the efficacy and uniformity of pazopanib. Considering these challenges, growing awareness has spurred a great deal of research on emerging drug delivery technologies. Current formulation strategies aim to enhance aqueous solubility, improve dissolution, reduce pH dependence, and maintain supersaturation in gastrointestinal fluids. The next section will take a critical look at these approaches in the formulation and evaluate their ability to maximize the bioavailability of pazopanib via the oral route, which is the primary route for the majority of oral drugs.

CONCLUSION

Pazopanib has emerged as an important oral, multi-targeted tyrosine kinase inhibitor in the oak field used to treat advanced renal cell carcinoma (RCC) and soft tissue sarcoma (STS). It has potent inhibitory activity against multiple angiogenic signaling pathways, including VEGFR, PDGFR and c-KIT, providing a greater treatment choice for patients with advanced malignancies. Although effective in therapy, the ability of pazopanib to yield therapeutic results has remained restricted due to less desirable, variable oral bioavailability. The poor oral absorption of pazopanib is primarily due to its low aqueous solubility, a characteristic of BCS Class II drugs, which have poor aqueous solubility and high intestinal permeability. The drug has a highly pH dependent solubility, being easily soluble in the acid pH of the stomach and poorly soluble in the more alkaline environment of the small intestine. Significant interpatient variability in systemic drug exposure also occurs because of other factors, such as slow dissolution,

the dependency of absorption on food, extensive plasma protein binding, first-pass hepatic metabolism, and interactions with acid suppressing drugs. The inter-individual variability in response to drug therapy and toxicity can consequently be very large even if the dose is the same, rendering dose optimization a treatment challenge that remains to be overcome.

Over the past decade, significant research efforts have been undertaken to devise formulation strategies to surmount them. Preclinical studies have shown that the use of amorphous solid dispersions, nanocrystals, polymeric nanoparticles, lipid-based drug delivery systems, self-emulsifying drug delivery systems, cyclodextrin inclusion complexes, mesoporous silica carriers and polymeric micelles have led to the improvement of the aqueous solubility, dissolution rate and oral absorption of drugs. Many of these technologies also allow for more consistent systemic exposure and allow drug absorption to be independent of the oral pH. A number of these types of delivery systems have shown promising data in laboratory and animal studies; fewer have been translated to a large-scale clinical trial. Thus, continued research is needed for long-term safety, ease of manufacture, regulatory acceptance, and clinical efficacy as compared to conventional formulations. Advanced pharmaceutical technologies and personalised therapeutic options should be integrated into future research. The synergy between rational formulation design, computational modelling, aid from artificial intelligence in optimizing formulations, physiologically based pharmacokinetic modeling, and therapeutic drug monitoring could pave the way for more personalized dosing and better treatment results. Moreover, additional clinical investigations with different clinical populations of patients and novel delivery systems are still required to untangle whether either the optimisation of the pharmacokinetic parameters or the decrease in toxicity will lead to better efficacy.

Improving the oral bioavailability of pazopanib remains a major challenge in pharmaceutical and clinical research in both drug and clinical development. The drug has a number of pharmacological activities for multiple angiogenic targets, however, to exploit the drug's therapeutic potential, this drug has to overcome the obstacles to efficient gastrointestinal absorption. Future improvements in drug delivery science, drug formulation and personalized medicine are anticipated to help overcome these barriers and further improve the safety, efficacy and clinical reliability of pazopanib therapeutic use.

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