



Crystallography and Biopharmaceutics of Some Antimalarials

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Authors' contributions

This work was carried out in collaboration among all the authors. Author SOA managed the literature search and wrote up the first draft. Author AOO scrutinized the write-up and did the approval of the final draft. Authors EFOE and MIA edited the second draft. All authors read and approved the final manuscript.

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ABSTRACT

Crystallography is a branch of science that deals with the discerning of the arrangement and bonding of atoms in crystalline solids. Crystal structural differences in the active pharmaceutical ingredient (API)/excipients in multi-source generics of antimalarials may present differences in their physicochemical properties and ultimately the rate and extent of drug absorption. Tackling the menace of the continuing spread of multi-drug resistant *Plasmodium falciparum* malaria may require the evaluation of the crystal structural influences of orally administered drugs on antimalarial bioavailability.

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1. INTRODUCTION

Combating the increasingly retractile malaria parasites should be approached from different angles [1,2]. Molecular description of resistance to the antiparasites has been characterized and is given to the structural changes in the target enzymes [3-5]. Most natural organic products of life are asymmetric and enantiomeric interactions with biological macromolecules (Easson-Stedman model) have been described [6]. Crystallographic studies have been exploited in pointing out differences in molecules that appear similar by other experiments. X-ray crystal structures have also accounted for unusual electronic or elastic properties of materials and served as a basis for designing pharmaceuticals.

Biopharmaceutics involve the study of the physico-chemical properties of a drug in its dosage form as it relates to the onset, duration, and intensity of drug action. It further explains the importance of factors that influence the protection and stability of the drug within the product, the rate of drug release from the drug product, rate of dissolution of the drug at the absorption site and its availability at its site of action. When a drug is administered orally, it is absorbed, distributed, metabolized and excreted. The characterization of the time course (kinetics) of these drug events is referred to as pharmacokinetics. Oral route is one of the major forms of drug administration. In oral dosing three factors affect absorption and consequently the bioavailability. These include physiological, physicochemical and formulation factors. Considering the wave of drug resistance development against antimalarial agents and the propagation/proliferation of multi-source generics, there is the need to closely monitor the various products with respect to the structural and polymorphic forms of the constituents (API and excipients), for salient and subtle differences that may affect performance [7]. The Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), the German drug regulation authority, issued guidelines for determining whether bioavailability/bioequivalence studies are required for certain drugs. This decision tree is based on pharmacodynamic, pharmacokinetic, and physicochemical criteria. Details of this decision tree were worked out by an expert panel named the Bioavailability Commission at the BfArM. The

decision tree has been in use by German regulatory authorities for more than 10 years now. In the meantime, its essentials were adopted by the European Committee for Proprietary Medicinal Products (CPMP) and by the World Health Organization (WHO) for their "Guidelines on interchangeability of multisource pharmaceutical products" [8-10].

1.1 Fundamental Concept of Crystallography

Majority of drugs are administered as solids hence the molecular structure and the solid state properties of the active ingredients influence the performance of the drug product [11]. A solid form of a drug can have very different solubility and dissolution profiles, depending on the crystalline form it exhibits. The more stable a crystalline form of a drug, the less soluble it is and this decrease in solubility can affect bioavailability. Most malaria drugs have not been studied to characterize their crystalline polymorphs in terms of their solubility and intrinsic dissolution. In cases where the amorphous form of a drug is known, a specially designed crystallization screening may be performed to improve the chemical purity and stability of the product [12,13]. When generic formulations of an approved drug are considered, care and appropriate evaluation of the API is required to select API that gives comparable bioavailability.

The instance of active erythro cinchona alkaloids (quinine and quinidine) and the inactive three forms (9-epiquinine and 9-epiquinidine) coupled with the apparent difference in susceptibility of *P. falciparum* to quinine and quinidine demonstrates the importance of three-dimensional structure to activity [11]. Recent reports have shown that the human pharmacokinetics of the individual (+) and (-) isomers of halofantrine differs with the (+) isomer attaining and retaining significantly higher plasma concentrations following oral administration (Table 1). Nobel Laureate Richard Feynman remarked that if the arrangements of things can be controlled, then the possible properties of the materials can be modulated to a greater extent and the range of applications to which it can be applied can be greatly enhanced [14]. Crystal engineering, therefore, is defined as the modeling, designing, synthesis and application of crystalline solids with redefined

and desired aggregation of molecules and ions [15-17]. The aim therefore of crystal engineering is to design and synthesize crystals so as to elicit one or more desired functional properties [11]. From the crystal studies, new phases of pharmaceuticals can be obtained with improved and optimized physical properties such as solubility, stability, dissolution rate, bioavailability and mechanical properties [18].

In the lawsuit of GlaxoSmithKline Beecham (GSK) against various generic companies concerning GSK's PAXIL® (Paroxetine), an antidepressant on which it owns a patent right licensed in 1920, the significance of adequate exploration of crystal structure was emphasized. The unstable anhydrate form which presented difficulties in the manufacturing process, led to the discovery of the hemihydrate form. GSK subsequently obtained patents in various countries to market "crystalline paroxetine hydrochloride hemihydrate". Apotex later filed for a notice of compliance ("NOC") to market the anhydrate form of paroxetine. GSK argued that the anhydrate was unstable and convertible to hemihydrate due to heat or humidity and adduced evidence of experiments showing that batches of anhydrate converted to hemihydrate over time. GSK further argued that its claim covered the hemihydrate in any amount. This issue of 'disappearing polymorph' in the packaging when exposed to heat or humidity and in fact on exposure to the patient's gastrointestinal juices was addressed as gastrointestinal infringement [19,20].

Solid state properties including polymorphism and salt formation can have a profound impact on important properties of drug products such as solubility and stability [21-22]. Many processes and product failures are traceable to a poor understanding and control of crystallization processes. It has been known from the middle of 10th century that many substances could be obtained in more than one crystal form [22] and the subject of drug polymorphism has received extensive attention but very little work has been done on antimalarial agents in the market today. The aspects of generic products registered for marketing in many African countries, gives the challenge of choice of polymorphs. The existence of non-bioequivalent products from the use of different polymorphs is a possibility [23,24].

The minimum building block of the crystal in a lattice is called the unit cell and this contains at

least one molecule. The symmetry considerations of the unique arrangement in space of the crystals are termed space groups and this symmetry usually show 230 unique arrangements which describe all the possible ways the different polymorphs manifest [22,25]. Molecular adducts include solvates, hydrates and a sub classification called clathrates (a special type of molecular adduct where the guest molecule occupy fully or is partially caged in the crystal lattice of the host [23,24,26]. Solvates and hydrates generally demonstrate different solubility and consequently different intrinsic dissolution rates compared to their unsolvated counterparts [23]. The inter-relationship of intrinsic solubility and dissolution on the bioavailability of drugs and the performance is the subject of the type of polymorph employed Figs. 1 and 2 [25,26].

1.2 Polymorphic Properties

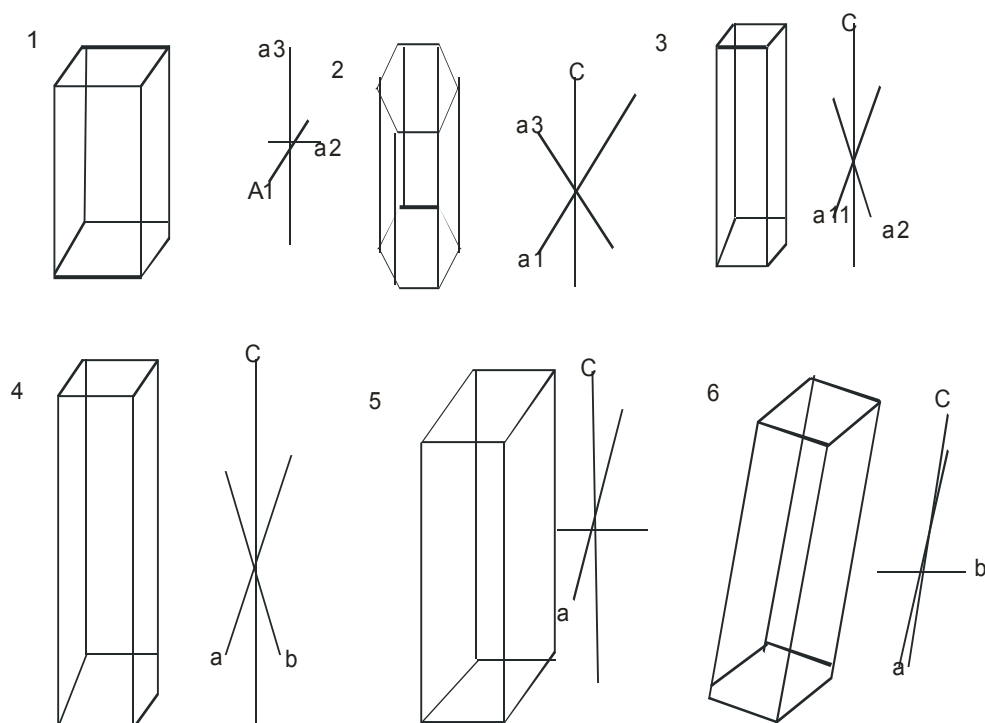
Crystalline solids existing as polymorphs, hydrates or solvates or the combinations of these can be classified as either enantiotropes or monotropes depending on the reversible transformation of one form to another that is possible under defined conditions of pressure and temperature [22,24]. Different crystal lattices can be formed by organic molecules through packing, orientation and conformational polymorphism. Packing polymorphism occurs when conformationally rigid arrangement is assembled into different three-dimensional structure through different intermolecular juxtapositions while conformational polymorphism occurs in flexible molecular arrangements bending into different conformations existing with alternative crystal structures [27]. The demonstration of chirality where the geometric and optical properties of a rigid object (*i.e.*, molecules of a drug) exist with mirror images that are not superimposable is a common biochemical phenomenon. More than half of all marketed drug molecule have one or more chiral centres therefore the racemate (*i.e.*, the two mirror images) or an enantiomer (*i.e.*, either of the mirror images) may have been assessed as an investigational new drug (IND) during pre-formulation studies. The enantiomers of a compound have the same chemical composition but different optical/ spatial orientation. This is the case with most antimalarial agents (Table 1). The physical properties of the API must be thoroughly characterized during drug development to provide a safe, efficacious and stable

pharmaceutical formula. Some chiral drugs are marketed as racemates, raceme conglomerate or pseudoracemates. Racemic compounds and pseudoracemates often comprise of heterochiral crystals. The differences in properties between the two enantiomers in a conglomerate and a racemic compound arise from the different interactions between the homochiral or

heterochiral molecules and from their different packing arrangements in the crystal structures [28,29]. These differences in crystal structures produce different physical properties and biological activities [28-30]. The application of these terms is important in modeling the tableting and compaction behaviour of drugs in pre-determined crystalline forms [23].

Table 1. Antimalarial agents, their structural presentation for malaria treatment and the observed biological activity attributable to their isoforms [11-13]

Antimalarial agents	Structural form of presentation	Possible relationship of structural forms	Comparing the activity of the enantiomers	Possible pharmacokinetic significance	Observed drug (isoform) action
Chloroquine	Racemate	Enantiomers	Not known	Not known	Not known
Mefloquine	Racemate	Enantiomers	Not defined	Significant	Cardioactivity
Halofantrine	Racemate	Enantiomers	(+)>(-) Halofantrine	Significant	Cardioactivity
Lumefantrine	Racemate	Enantiomers	Not known	Significant	Not known
Quinine	Racemate	Diastereoisomers	Quinidine >quinine	Not known	Cardioactivity



1. Isometric (cubic) a_1, a_2, a_3 at angle 90° ; 2. Hexagonal; a_1, a_2, a_3 at 90° ; 3. Tetragonal, a_1, a_2, a_3 at 90° ; 4. Orthorhombic, a, b, c at angle 90° ; 5. Monoclinic, angles between a & b , b & $c = 90^\circ$ and between a & c at angle 90° ; 6. Triclinic, a, b, c at angle 90°

Fig. 1. Crystal Lattices and their structural arrangements [25]

1.3 Instrumentation in crystallography

There are a number of analytical equipments and techniques primarily used for phase identification of crystalline materials. Fig. 3 gives a schematic diagram of the basic operations of crystallographic analyzers [31,32]. Single crystal X-ray diffractometry is most widely used for the identification of unknown crystalline materials and is currently applicable to assessing biological performance of known chemical entities as it defines sample purity [33]. When a satisfactory crystal is produced, the crystal structure is determined by single crystal x-ray diffractometer (SCXRD). Crystals diffract x-rays in a pattern that is unique to the respective crystals and depends on their internal structures [34,35].

The intensities and the phases of the diffracted x-rays are employed for the crystal structure determination. The intensities can be determined directly from the diffraction pattern. The crystal structure is elucidated by observing the unit cell type and the space group by acquiring a far diffraction frame and observing the pattern for missing diffraction intensities referred to as systematic absences. The knowledge of the space group can help simplify the analysis of the diffraction pattern and reveal the important symmetry elements within the unit cell. In difficult cases due to the non availability of suitable crystals, computational techniques can be utilized to predict crystal structure [36,37]. Determination of the crystal structure by conventional SCXRD requires crystals of suitable size and quality. In general, the minimum dimension along each axis of the crystal should exceed 0.05 mm, unless a heavy atom is present in the constituent molecules [38]. X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material. Max von Laue in 1912 discovered that crystalline substances act at three-dimensional diffraction gratings for X-ray wavelengths similar to the spacing of planes in a crystal lattice [39]. X-ray powder diffraction is most widely used for the identification of unknown crystalline materials and is currently applicable to biological performance of known chemical entities as it defines sample purity [40].

The use of scanning electron microscopy (SEM) generates a variety of signals that reveals information about the sample employed including the external morphology (texture), chemical composition and crystalline structure through the analysis of 2-dimensional image and its

corresponding spatial variations [41,42]. Multi-collector-inductively Coupled Plasma Mass Spectrometer (MC-ICPMS) is an instrument that measures the isotopic ratios that make up the sample. This is extensively used in geochemistry, geochronology and cosmochemistry and now applicable to biopharmaceutics to explain the possible differences in biological performance of samples of drugs [43,44].

Another analytical device called secondary ion mass spectrometer (SIMS) uses an internally generated beam of either positive or negative ions called primary beam focused on a sample surface to generate a secondary ion across a high electrostatic potential. This enables the surface analysis of organic compounds. The extension of geochemical instrumentation and analysis to biopharmaceutics can also explore the principles of instrumental neutron activation analysis (INAA) to determine the concentration of trace and major elements in a variety of matrices through the introduction of a neutron flux and production of radioactive nuclides [45].

Fourier transform infra red spectroscopy (FTIR) is most useful for identifying chemicals that are either organic or inorganic. The term FTIR refers to a fairly recent development in the manner in which the data is collected and converted from an interference pattern to a spectrum. FTIR is computerized and this makes it more sensitive and faster than the older dispersive instruments. FTIR can be used to identify chemicals from polymers, drugs and contaminants. FTIR is perhaps the most powerful tool for identifying the types of chemical bonds or functional group present in samples [46].

Synchrotron includes an electron accelerator that uses synchronized magnetic fields and the use of high speed electrons directed to collide with an appropriate target to produce high energy x-ray or UV radiations. When a solid is heated beyond its melting temperature, it fuses (melts) to produce a liquid that can be called a melt. The crystal structure of the solid is thus determined at the molten state [47]. This enables the surface analysis of organic compounds. Sourier transform infrared spectroscopy (STIR) is most useful for identifying chemicals that are either organic or inorganic. The term refers to a fairly recent development in the manner in which the data is collected and converted from an interference pattern to a spectrum [11,31]. Various combinations of the above technique can

also be employed in a systematic manner to rapidly screen polymorphs, solvates and salt forms.

1.4 Crystal Structure Prediction

Since 2007, significant progress has been made in the crystal structure prediction of small organic molecules, with several different methods proving effective. The ultimate goal in crystal structure prediction is to predict the crystal structure from the molecular structure of a compound. This involves the calculation of the lattice energies of molecular crystal followed by ranking of these structures according to their structural stabilities. In the isomorphs replacement method, a heavy atom is introduced into the crystal lattice without disrupting the original crystal structure in order to predict the crystal structure and thereafter the biological permeability factors for optimum therapeutic effectiveness are investigated [41].

2. BIOPHARMACEUTICS

This explains how the physicochemical properties of drugs, dosage forms and routes of administration affect the bioavailability (*i.e.*, the rate and extent of drug absorption). Thus, biopharmaceutics involves factors that influence the protection and stability of the drug within the product; the rate of drug release from the product, the rate of dissolution of the drug at the absorption site and the availability of the drug at its site of action. The oral route is an important means of drug administration hence it is pertinent to consider the factors that affect the bioavailability of drugs through this route. There are physiological, physicochemical and formulation factors considered in this subject. Physiological factors affecting oral absorption include membrane physiology, passage of drugs across membranes and gastrointestinal physiology. The characteristics of GIT physiology as it concerns drug absorption relates to gastric emptying time and motility and the effect of food on drug absorption. The evaluation of drug performance parameters such as the minimum effective concentration (MEC), minimum toxic concentration (MTC), onset time (the time required for the drug to reach the MEC), duration of action (the difference between the onset time and the time for the drug to decline back to the MEC), area under the plasma time curve (AUC), peak plasma level (C max) and time to achieve the peak plasma level (t max) are all indices to the rate and extent of drug absorption. Since

biopharmaceutics delves into the inter-relationship of the physicochemical nature of the active pharmaceutical ingredients, the dosage form, the environmental influence on drug release, crystallography can be exploited to point out the structural differences in the molecules of the same API that can influence its physicochemical nature in that formulation or in the route of administration [48].

2.1 Physicochemical Factors Affecting Oral Absorption

One important property of drug is their PH partition characteristics which affects their membrane permeability. Most drugs are weak electrolyte with varying degrees of ionization in solution. The unionized form of weakly acidic/basic drug (lipid soluble form) will pass across the gastrointestinal epithelia while the ionized (poorly lipid soluble fraction) is impermeable. The extent to which a weakly basic or acidic drug ionizes in solution in the gastrointestinal fluid may be calculated by the Henderson-Hasselbalch equation [49].

$$-Log K_a = -Log [H^+] - Log [A^-]/[HA] \quad (1)$$

$$PK_a = PH - Log \frac{[A^-]}{[HA]} \text{ For weak acids } (2)$$

$$PK_a = PH + Log \frac{[HB^+]}{[B]} \text{ For weak base } (3)$$

Furthermore, some drugs are poorly absorbed after oral administration though they are unionized in the small intestine. This can be explained by the principle of partition coefficient (P) of the drug [50].

$$P = \frac{[D]_{lipid}}{[D]_{water}} \quad (4)$$

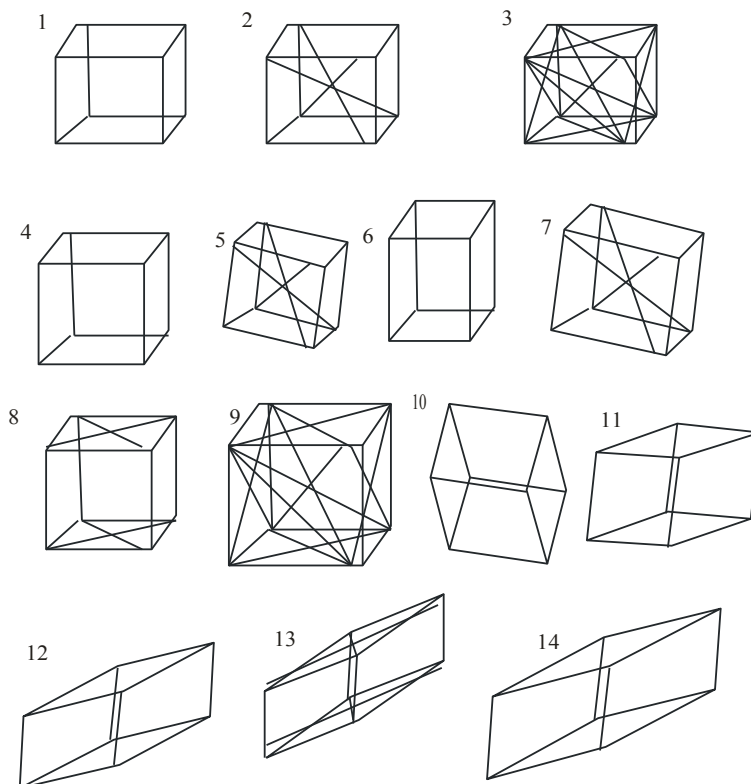
Where D_{lipid} and D_{water} are concentration of drug in the lipid and water phases respectively.

In many instances the dissolution step is the rate limiting step in drug bioavailability process. The dissolution of drugs in the gastrointestinal tract was described by Fick's law [51].

$$\text{Rate of dissolution} = D.A [C_s - C_h]/h \quad (5)$$

Where D is the diffusion coefficient (related to the viscosity of the diffusion medium, the molecular size and the lipid solubility of the drug), A is the

surface area of the medium, h is the thickness of the diffusion layer and $(C_s - C_h)$ is the concentration gradient, with C_s and C_h being the concentrations of the drug in the absorptive medium and the blood, respectively.



1.Simple cubic; 2. Body centered cubic; 3. Face centered cubic; 4. Simple tetragonal; 5. Body centered tetragonal, 6. Simple orthorhombic; 7. Body centered orthorhombic; 8. Base centered orthorhombic 9. Face centered orthorhombic; 10.Rhombohedral; 11. Hexagonal; 12. Simple monoclinic; 13. Body centered monoclinic ; 14. Triclinic.

Fig. 2. Dimensional lattices of crystals [25]

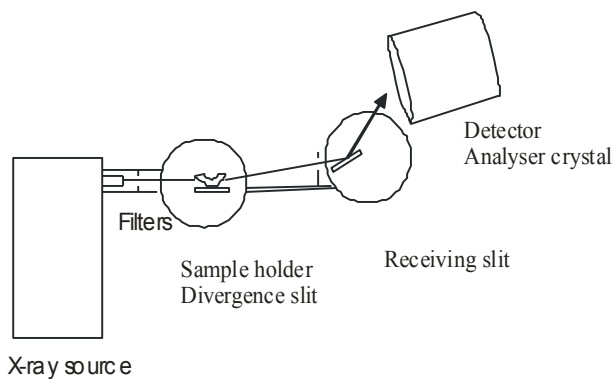


Fig. 3. The schematic diagram of the crystallographic analyzers [31]

In manufacturing, the particle size of the API and surface area presented for dissolution is proportional to the dissolution rate provided the critical point of particle size reduction where clumping together of particle have not been exceeded.

The salt forms of an API may have differing intrinsic aqueous solubility. Salts of weak acids/base generally have higher aqueous solubility than the free acids or bases. The crystalline forms in which a drug exists determine its stability and solubility properties in the gastrointestinal tract. Drugs can be presented in different polymorphic forms and there can be reversion of an unstable form to a stable polymorph altering the physicochemical properties earlier envisaged. A follow up on the biopharmaceutics and pharmacokinetic parameters of the choice of polymorph employed in formulation will go a long way to delivering a consistent concentration of drug in cases of multi-source generic or batch to batch production of drugs.

2.2 Effect of Formulation Factors on Bioavailability

The outcome of any production can be complex based on the physicochemical nature of the API, the ingredients employed and the methods of handling. The additives often employed are lubricants which are hydrophobic; granulating agents (employed to stick the ingredients together); filler to bulk up the weight of the drug; wetting agents to facilitate the penetration of water into the tablet and disintegrating agents to help break the tablet apart prior to dissolution. The manner of incorporation and the amount employed of these agents determine the drug release pattern of the drug product [23].

Absolute bioavailability (F) compares the bioavailability estimated as area under the curve or AUC of the active drug in the systemic circulation following non-intravenous administration (*i.e.*, oral, rectal transdermal, subcutaneous administration *etc.*) with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. This ranges from F =0 (no drug absorption) to F =1 (complete drug absorption). Relative or comparative bioavailability refers to the availability of a drug product as compared to

another dosage form or product of the same drug given in the same dose. This measurement determines the effects of formulation differences on drug absorption. In most cases the principle of calculation is to compare the respective AUC of the products. Pharmaceutical alternatives refer to drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Pharmaceutical equivalent: means drug products that contain identical amounts of the identical active drug ingredient (*i.e.*, the salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times and/or dissolution rate).

2.3 Characteristics of GI Physiology and Drug Absorption

2.3.1 Mechanisms of absorption

Several mechanisms exists for drug absorption in the GI, these include the carrier mediated (specialized carrier molecule motivated, movement against concentration gradient, energy requiring and non-saturable transport process), facilitated diffusion (carrier mediated, non-energy driven, saturable transport process) and passive diffusion (non-energy driven, non-saturable transport process). By the absorptive membrane is a more or less stagnant layer of water and mucous adjacent to the intestinal wall. This layer can provide a diffusion barrier to drugs [32]. This relationship is expressed by Fick's law of diffusion.

$$\text{Rate of Diffusion} = -D.A.(C_s - C_h)/x \quad (6)$$

Here D is diffusion coefficient, A is surface area of the intestinal lining, x is the thickness of the absorption membrane thickness while C_s and C_h are the concentration of drug in the GIT and the blood, respectively [52].

2.3.2 Patient/host - related modalities

The time a dosage form takes to traverse the stomach is usually described by the gastric residence time, GE time or GE rate. Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the

stomach; therefore quicker stomach emptying will increase drug absorption. For example, a good correlation has been found between GE time and peak plasma concentration for acetaminophen. The faster the GE for a drug in the gastrum (*i.e.*, shorter GE time), the higher the plasma concentration that is achieved for that drug. Also GE can lead to increased degradation of drugs in the stomach because of the low pH. The presence of food in the GIT can influence the rate and extent of absorption. Complexation of drugs with components in the diet e.g. tetracycline forms non-absorbable complexes with calcium and iron thus retarding its absorption [52].

Food tends to increase stomach pH by acting as a buffer. This is liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one. The presence of food may cause an increase in the viscosity of the dissolution medium leading to a decrease in the rate of diffusion away from the surface of drug and ultimately giving a decrease in dissolution rate. Table 2 summarizes the effect of food and other factors on gastric emptying of gastric content after oral dosing.

'Biorelevant media' were first introduced by Jennifer Dressman in 1998. The idea was to improve conventional dissolution media by making them resemble intestinal fluids closely. Prior - existing dissolution media only simulated pH [53]. Important factors such as osmolarity and buffer capacity were absent; natural surfactants (bile salts and lecithin) found in bile were also missing. These natural surfactants affect drug solubility, particularly if the drug is poorly soluble. Importantly, biorelevant dissolution media contain these natural surfactants for a more accurate simulation of the fluid in the human gastrointestinal tract. There are biorelevant media to simulate fluid in the GI tract both before ('Fasted') and after ('Fed') food is eaten. For drugs presented in immediate release formulations, Fasted State Simulated Intestinal Fluid ('FaSSIF') is more commonly used to test drug dissolution. This is because drugs typically have to dissolve in this fluid if they are to be absorbed in the small intestine without food. If the 'Fed State' is required for drug dissolution, tests in Fed State Simulated Intestinal Fluid ('FeSSIF') is carried out. Though originally intended for drug dissolution, the use of these media has been extended to test the solubility of new potential drug entities in discovery. Biorelevant media are now being used in the

Pharmaceutical industry much more frequently due to the increasing number of poorly water soluble drugs on the market which require more accurate simulations of the solubilization process *in vitro*. This is important for the formulation development of new drugs and vital when developing oral formulations of generic drugs that are intended to be bioequivalent [54].

Table 2. Food related factors affecting GE time [52]

Factors	Effect on GE
Food related factors	
Volume of ingested material	GE increases with increase in gastric content
Fatty meal ingestion	GE decreases
Carbohydrate meal ingestion	GE decreases
Temperature of food	
Hot food	GE increases
Cold food	GE decreases
Drug related factors	
Anticholinergic drugs	GE decreases
Analgesic	GE decreases
Disease state	
Hypothyroidism, diabetes	GE increases

NB: Increased GE is synonymous with short transit time

3. THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and permeability. It allows for the prediction of *in vivo* pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes (Table 3) based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form. The interest in this classification system stems largely from its application in early drug development and then in the management of product change through its life cycle. In early drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stop its development. Therefore, an organization wishing to produce oral dosage forms will wish to limit development to molecules with high permeability (Table 3). Increasingly, these considerations are incorporated from the very earliest phases, with the concept of property-based design being used in combinatorial chemistry to target production of

compounds showing optimal properties. This classification is associated with a drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers. [55].

Table 3. Classification of drugs (BCS) [50]

Classification	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Dissolution performance is influenced by both the physicochemical properties of the substance and the prevailing physiological conditions in the GI tract, which varies between the fasted and fed states as well as within and among subjects. The key *in vivo* parameters influencing drug product dissolution performance are summarized in Table 4.

4. CRYSTALLOGRAPHY AND BIOPHARMACEUTICS OF SOME ANTIMALARIAL DRUGS

The spread of multi-drug resistant *P. falciparum* malaria will require the development of new antimalarial drugs that can combat the protozoa. Another angle of tackling the problem may be directed at re-engineering efforts that refine the existing antimalarial agents from the three-dimensional perspective. The enhanced biochemical and biopharmaceutical potentials of the products will give better activity profile. This may be what is expected to give the anticipated answer to the long standing warfare against resistant malaria [56].

4.1 Halofantrine

The absolute configuration of the single chiral centre in (-) halofantrine was established to be the S configuration. Thus (+) halofantrine, the more cardiotoxic isomer, has the R Configuration. The C atom adjacent to the aromatic ring has the same configuration in both (+) halofantrine and quinidine suggesting a stereospecific component to the cardiotoxicity produced by both agents [48,56]. Pharmacokinetic information on halofantrine is limited but it is suggested that halofantrine HCl in its racemic form, the currently available formulation, is poorly and erratically absorbed from the GIT as a result of its limited solubility.

Reports have shown that the human pharmacokinetics of the individual isomers of halofantrine differ, with the (+) isomer attaining higher concentration than the (-) isomer in plasma following oral administration. In rat liver homogenate, it was shown that the (-) isomer was preferably metabolized [57].

4.2 Mefloquine

The absolute configuration of mefloquine has been established as 11R, 12S by X-ray crystallography of the hydrochloride salt. (-) - mefloquine has the same stereochemistry as quinine and (+) - mefloquine has the same stereochemistry as quinidine [58]. The potency of (+) mefloquine for antimalarial activity was reported to be more than (-) mefloquine. The crystal of (-) mefloquine HCl contained four different conformations which mainly differ in a small rotation of the piperidine ring. These conformations have been shown to be same as the crystalline conformations of racemic mefloquine free base, mefloquine HCl and methylsulfonate monohydrate [54-56].

Table 4. Physicochemical and physiological parameters important to drug dissolution in the gastrointestinal tract [55]

Factors	Physico-chemical Parameters	Physiological Parameters
Surface area of drug	Particle size and wettability	Surfactants in gastric juice or bile
Diffusibility of drugs	Molecular size	Viscosity of luminal fluid
Boundary layer thickness	Concentration of the drug	Motility pattern and flow rate
Solubility	Hydrophilicity, crystal structure and solubilization	pH, buffer capacity, bile and food composition
Amount of drug already dissolved	Hydrophilicity, lipophilicity and nature of the drug	Permeability
Volume of solvent available	Dependent on type of body fluid	Secretion and co-administered fluid

4.3 Lumefantrine

According to Table 1, lumefantrine is marketed as a base and a racemic mixture [53]. The literature on the activity of the individual enantiomers of lumefantrine is very limited. The three dimensional studies of the enantiomers may reveal pharmacological differences that can be exploited for optimal antimalarial activity.

5. FINAL REMARKS

The biopharmaceutical inequivalence noticeable on analysis of generic products is possibly pivotally rested on the structural differences presented by the API. Three dimensional data can make the structural differences responsible for variations in biological activity among generic products vivid. Recently, single enantiomeric forms of chiral drugs are increasingly marketed as improved chemical entity with demonstrable better pharmacological profile while traces of the other enantiomer are considered as enantiomeric impurity as treated accordingly as other organic impurities. The resistance to artemisinin based combination drugs that is being reported in some part of the globe can be investigated from the crystallographic studies of the generic products available in the market.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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