Journal of Pharmaceutical Sciences 110 (2021) 1935-1947

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Carbamazepine

Mauricio A. García [a], Rodrigo Cristofoletti [b], Bertil Abrahamsson [c], Dirk W. Groot [d], Alan Parr [e], James E. Polli [f], Mehul Mehta [g], Vinod P. Shah [h], Tajiri Tomakazu [i], Jennifer B. Dressman [j, **], Peter Langguth [a, *]

[a] *Pharmaceutical Technology and Biopharmaceutics, Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Mainz, Germany*
[b] *Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA*
[c] *Pharmaceutical Development, AstraZeneca R&D, Mölndal, Sweden*
[d] *RIVM (National Institute for Public Health and the Environment), Bilthoven, the Netherlands*
[e] *BioCeutics LLC, Cary, NC, USA*
[f] *Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD, USA*
[g] *Division of Clinical Pharmacology, Centre for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, USA*
[h] *International Pharmaceutical Federation (FIP), The Hague, the Netherlands*
[i] *Pharmaceutical Science & Technology Laboratories, Astellas Pharma Inc, Ibaraki, Japan*
[j] *Fraunhofer Institute of Translational Medicine and Pharmacology, ITMP, Institute of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany*

ARTICLE INFO

Article history:
Received 29 December 2020
Revised 28 January 2021
Accepted 3 February 2021
Available online 18 February 2021

Keywords:
Carbamazepine
Biowaiver
Solubility
Permeability
Biopharmaceutics classification system (BCS)
Dissolution
IVIVC
Narrow therapeutic index

ABSTRACT

Literature relevant to assessing whether BCS-based biowaivers can be applied to immediate release (IR) solid oral dosage forms containing carbamazepine as the single active pharmaceutical ingredient are reviewed. Carbamazepine, which is used for the prophylactic therapy of epilepsy, is a non-ionizable drug that cannot be considered "highly soluble" across the range of pH values usually encountered in the upper gastrointestinal tract. Furthermore, evidence in the open literature suggests that carbamazepine is a BCS Class 2 drug. Nevertheless, the oral absolute bioavailability of carbamazepine lies between 70 and 78% and both *in vivo* and *in vitro* data support the classification of carbamazepine as a highly permeable drug. Since the therapeutic and toxic plasma level ranges overlap, carbamazepine is considered to have a narrow therapeutic index. For these reasons, a BCS based biowaiver for IR tablets of carbamazepine cannot be recommended. Interestingly, in nine out of ten studies, USP dissolution conditions (900 mL water with 1% SLS, paddle, 75 rpm) appropriately discriminated among bioinequivalent products and this may be a way forward to predicting whether a given formulation will be bioequivalent to the comparator product.

Introduction

Carbamazepine is commonly used to prevent seizure episodes in patients diagnosed with epilepsy, as well as to relieve the pain associated with trigeminal neuralgia. The World Health Organization (WHO) includes immediate release (IR) tablets containing carbamazepine as an anticonvulsant/antiepileptic drug in lists of essential medicines (EML) for both adults and children.[1–3] Additionally, the 21st edition of WHO EML for adults also recommends carbamazepine IR tablets as a treatment for behavioral disorders.[2]

A Biowaiver Monograph based on the available literature is presented for carbamazepine. The purpose and scope of these monographs have been previously discussed in detail.[4] To date, more than 45 biowaiver monographs have been published, which are all available on-line at www.fip.org/bcs_monographs.[5] Briefly, these aim to summarize and evaluate all data relevant for the

* Corresponding author. Pharmaceutical Technology and Biopharmaceutics, Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Staudingerweg 5, 55099 Mainz, Germany.
** Corresponding author. Institute of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany.
E-mail addresses: dressman@em.uni-frankfurt.de (J.B. Dressman), langguth@uni-mainz.de (P. Langguth).

https://doi.org/10.1016/j.xphs.2021.02.019
0022-3549/

decision as to whether IR oral dosage forms containing the active pharmaceutical ingredient (APIs) could be approved according to the BCS-Biowaiver methodology, rather than having to undergo a pharmacokinetic evaluation of bioequivalence with a comparator formulation in a clinical study. APIs which are listed on the WHO EML,[2] have priority for this evaluation, since they are used in many countries where a clinical study might be onerous. The BCS-based biowaiver methodology, by contrast to pharmacokinetic-based bioequivalence studies, enables products to be evaluated using dissolution testing in order to assess bioequivalence, thus enabling new medicines to be brought to market more quickly and at less expense. However, the guidances[1,6–8] that have been issued to regulate the application of the BCS-based biowaiver must be followed to apply the BCS-based biowaiver methodology, with consideration not only of the solubility and permeability elements of the BCS but also wider clinical questions such as whether the API has a wide or narrow therapeutic index (NTI) and whether the benefits of applying the BCS-based biowaiver approach outweighs any potential risks associated with its application.

In the present monograph, the risk of waiving *in vivo* bioequivalence (BE) studies, by *in vitro* studies, in the approval of new and/or reformulated carbamazepine drug products manufactured as IR solid oral dosage forms is assessed.

Methods

Published information was obtained from PubMed, up to October 2020, and through the International Pharmaceutical Abstracts. Key words used were: carbamazepine, indications, therapeutic index, solubility, polymorphs, partition coefficient, permeability, absorption, distribution, metabolism, excretion, bioavailability, bioequivalence, dissolution, IVIVC, and excipients. Whenever appropriate, original literature based on the references in any given report was consulted.

General Characteristics

The chemical structure of carbamazepine is shown in Fig. 1. According the IUPAC nomenclature, its name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide.[9,10] However, it can be also found under the chemical name: 5H-Dibenz[b,f]azepin-5-carbamide. Carbamazepine molecular formula is $C_{15}H_{12}N_2O$, its molecular weight (MW) is 236.3 g/mol and it is registered under the Chemical Abstracts Service (CAS) number: 298-46-4.[10] Visually, carbamazepine corresponds to white to yellowish-with crystalline powder that melts between 189 and 193 °C. The powder is very slightly soluble in water, freely soluble in dichloromethane and sparingly soluble in either acetone or ethanol 96%.[9]

Therapeutic Indication &Therapeutic Index

Carbamazepine is indicated in the prophylactic treatment of different types of epilepsy (partial and generalized tonic-clonic seizures), as well as to relieve pain related to trigeminal neuralgia.[11,12] The mechanisms of action have not yet been fully understood. However, a decrease of polysynaptic responses together with the blockage of post-tetanic potentiation seem to be involved in the prevention of seizures. This would depress the action potential in both the thalamus and polysynaptic reflexes (by binding to voltage-dependent sodium channels).[11,13]

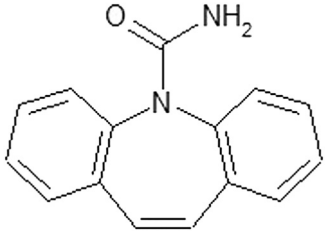

Fig. 1. Chemical structure of carbamazepine.

Conventionally, the therapeutic range for serum carbamazepine levels has been defined as 4–12 μg/mL.[14,15] However, diverse attempts to correlate either therapeutic or adverse effect with plasma concentrations have led to contradictory outcomes.[16,17] Newly diagnosed patients became seizure free at plasma concentrations lower than 8 μg/mL, although seizure control in certain individuals was also seen at plasma levels as low as 1.7,[16] or even at 1.2 μg/mL.[14,18] By contrast, Lesser et al. reported that around 50% of patients with intractable seizures responding to treatment showed plasma concentrations from 9.7 to 12.5 μg/mL, whereas practically the same plasma levels were found in patients whose epilepsy was not well controlled. Furthermore, the authors showed that serum concentrations of patients with and without adverse effects ranged between 7–12.3 and 9.4–17.2 μg/mL, respectively.[19]

Common adverse effects related to carbamazepine encompass central nervous system, hematologic, gastrointestinal and cutaneous symptoms.[15,20,21] A systematic review of diverse clinical studies indicated that somnolence, gastrointestinal symptoms and rash showed the highest incidences (26, 29 and 32%, respectively) in patients treated with 200–2000 mg.[22]

Consistently, adverse reactions have been detected within the range 5.9–8.3 μg/mL,[23,24] similar to the serum concentrations at which carbamazepine is used for the treatment of epilepsy. For instance, mean plasma levels at steady state (C_{ss}) of 6.52 μg/mL were reported after three weeks of treatment with 200 mg of the reference product three times a day.[25] Although that value must therefore considered to be within the therapeutic range, adverse effects have been reported at plasma levels at and above 5.9 μg/mL.[23,24]

With respect to cutaneous symptoms, the appearance of toxic epidermal necrolysis and Stevens-Johnson syndrome have both been related to carbamazepine. The risk of these events is estimated ten-fold higher in Asian than Caucasian populations, very likely due to a variant in the HLA-B gene (HLA-B*1502).[11] With respect to hematologic adverse effects, aplastic anemia and agranulocytosis have been associated with the use of this drug.

Interestingly, Olling et al. demonstrated that adverse effects (dizziness, fatigue, drowsiness, among others) occurred in a single dose BE trial at a dose of two 200 mg IR carbamazepine tablets. In this report, C_{max} of drug products ranged from 2.6 to 3.5 μg/mL, whereby faster absorbing formulations tended to evoke a higher occurrence of adverse effects.[26] Tothfalusi et al. further confirmed those findings by introducing a PK/PD model with the data already published by Olling et al. Good correlations between the partial AUC (AUCP) parameter of various bioinequivalent products and incidences of adverse events were observed.[17] However, it may be difficult to generalize these findings, since overlaps between therapeutic and toxic doses have been consistently reported in the literature.

Carbamazepine poisoning has been reported to occur after exposure to doses over 1400 mg, and it was mainly characterized by neurologic symptoms, namely, altered mental status, decreased consciousness, and recurrent seizures. Additionally, systemic consequences such as respiratory depression, hypotension and dysrhythmias have been observed.[15] Fatal outcomes have been associated after ingesting above 20 g orally.[15,21]

Given the therapeutic range from 4 to 12 μg/mL,[14] a therapeutic index of 3 can be calculated. Nevertheless, this value may actually

overestimate the reality since: i) therapeutic and toxic doses overlap, and ii) the therapeutic range of individuals could be even narrower.[22] Therefore, carbamazepine is considered to be a narrow therapeutic index (NTI) drug. This classification is further supported by the FDA in its draft guidance on carbamazepine, which considered these arguments, together with the need for therapeutic monitoring and low-to-moderate within subject variability.[27]

Dose, Dosage Forms and Strengths

Initially, carbamazepine 200 mg IR tablets twice daily are recommended in the treatment of epilepsy. Doses should be gradually increased by up to 200 mg weekly, leading to a regime of 200 mg three- or even four-times daily. Individual titration of the patient is also suggested, although typical maintenance doses consist of 800–1200 mg daily.[11,12] In special cases, daily doses as high as 1600 mg can be used.[11] Even though daily doses of 300–1400 mg have shown efficacy in seizure control,[23,28] no clear correlation has been observed between dose administered and efficacy.[20,22] On the other hand, 100 mg b.i.d. is recommended in the palliative treatment of trigeminal neuralgia, which can be increased up to 400–800 mg daily as maintenance doses.[11]

Carbamazepine drug products with market authorizations (MA) encompass intravenous (IV) solutions 200 mg/20 mL, oral suspensions (100 mg/5 mL), chewable tablets (100, 200 mg), immediate release tablets (100, 200, 300, 400 mg), extended release capsules (100, 200, 300 mg) and extended release tablets (100, 200, 400 mg).[29] Among them, only few presentations are listed in both the adult and pediatric WHO EML. Carbamazepine is stated as an anticonvulsant/antiepileptic medicine in both the 7th (children) and 21st (adults) EML when formulated as oral liquid (100 mg/5 mL), chewable tablets (100, 200 mg) and (scored) tablets (100, 200 mg).[2,3] This latter dosage form was also included in the EML as a treatment of bipolar disorders in adults.[2] In turn, the carbamazepine monograph in the U.S. Pharmacopeia (USP) includes oral suspensions (100 mg/5 mL), chewable tablets (100 mg), immediate release tablets (200 mg) and extended release tablets (100, 200, 400 mg).[10]

Physicochemical Properties

Polymorphs & Hydrates

Four anhydrous polymorphs and two dihydrates of carbamazepine have been extensively characterized.[30–33] According to the unified nomenclature proposed by Grzesiak et al., triclinic and trigonal polymorphs (forms I and II, respectively) share very similar crystal packing,[31,33] and needle-like morphology.[34,35] On the other hand, the P-monoclinic and C-monoclinic forms (III and IV, respectively) are also related to each other.[31] Similar to Forms I and II, carbamazepine dihydrate (DH) displays a needle-like form.[36,37] However the DH can be easily distinguished from either Form I or II given that the former exhibits a molecular weight approx. 13% higher at the same content of carbamazepine than the anhydrous forms.[34]

Power X-ray diffraction (PXRD) and differential scanning calorimetry (DCS) are powerful tools for discriminating among carbamazepine polymorphs.[31,33] Form I shows characteristic peaks in PXRD between 7.9 and 9.4 [2θ°], as well as several others at 12.3, 13.2, 19.9 and 22.9 [2θ°]. As for DCS, the scan of Form I shows just one endotherm in the range 189–191 °C, corresponding to its melting range.[30,31] This melting range can be also observed for the DH, and both Forms II and III. Nevertheless, these latter polymorphs showed additional endotherms before the peak, at 191 °C, which are not observed for form I. Flicker et al. characterized four different marketed products of IR carbamazepine, finding that Forms I and III were the most prevalent.[38]

Solubility

Numerous carbamazepine solubility data have been reported in the literature.[39–47] Given the biopharmaceutic aim of this monograph, Table 1 summarizes solubility data obtained at body temperature, i.e. at 37 °C. The presence of 0.5 or 1% sodium lauryl sulfate (SLS) increases carbamazepine solubility by approx. five- or ten-fold, respectively. The solubility of carbamazepine appears to be insensitive to effects of either buffer or pH. The Dose/Solubility ratio in SLS-free media was always reported to be higher than 580 mL (based on the highest strength in the WHO EML: 200 mg).[1] However, this ratio may be even larger if either the highest clinical

Table 1
Solubility of Carbamazepine in Different Media at Temperature 37 °C.

Media	pH	Sodium Lauryl Sulfate (SLS %)	Solubility (mg/mL)	D/S[a] (mL)	Reference (Ref)
Unbuffered		Absence			
Water	–	–	0.24	833[b]	44
Water	–	–	0.24	833[b]	40
Buffered		*Absence*			
HCl 0.1 N	1	–	0.34	588[b]	43
HCl 0.1 N	1	–	0.26	782[b]	46
SGF	1.2	–	0.24	849[b]	46
FaSSIF	6.5	–	0.24	847[b]	47
SIF	6.8	–	0.24	841[b]	46
HIF	6.5–7.5	–	0.28	707[b]	47
Unbuffered		*Presence*			
Water	–	0.5	1.50	133	44
Water	–	0.5	1.29	155	46
Water	–	1	2.94	68	46
Water	–	1	2.50	80	44
Water	–	1	2.04	98	43
Buffered		*Presence*			
Phosphate buffer	4	0.5	1.30	133	44
Phosphate buffer	6.8	0.5	1.40	154	44
Phosphate buffer	4	1.0	2.40	83	44
Phosphate buffer	6.8	1.0	2.40	83	44

SGF, Simulated gastric fluid; SIF, Simulated intestinal fluid; FaSSIF, Fasted state simulated intestinal fluid; HIF, Human intestinal fluid.
[a] For 200 mg = the highest tablet strength in the WHO Essential Medicines List, 21st Ed.
[b] Outside the critical limit of <250 mL.

dose or highest strength in the market (400 mg) are considered. As a result of its poor aqueous solubility, many attempts to increase carbamazepine solubility by applying diverse technologies such as co-crystals can be found in the literature.

Partition Coefficient

Calculated partition coefficient (CLogP) values of 1.98,[42] 2.28,[48] and 2.25,[49] have been reported using different computational approaches. Consistently, a LogP of 2.93 has been estimated by atomic contributions-based methods.[42] By contrast, a partition coefficient of 1.51 determined by shake flask methods was slightly lower than the computational values.[49] Overall, the literature suggests a higher affinity for lipids versus the aqueous phase.

pKa

Two relatively high pKa values have been published by two different authors (11.83 and 14),[49,50] probably belonging to the equilibrium $R{-}NH_2 \leftrightarrow R{-}NH^- + H^+$. Therefore, no ionization is expected for carbamazepine within the physiological pH range. This is in good agreement with the lack of pH-dependence of carbamazepine's solubility within the physiologically relevant pH range (Table 1).

Pharmacokinetic Properties

Absorption and Bioavailability

Faigle and Feldmann administered gelatin capsules containing ^{14}C-labeled carbamazepine orally to two healthy subjects. The authors found that 72% of the dose was recovered in the urine, while the remaining 28% was recovered in the feces.[51] Two decades later, Gérardin et al. prepared in-house IV solutions to study the absolute BA of 2% of ^{15}N-labeled suspensions in two healthy volunteers. Using this approach, absolute BA values of 100.1 and 102.3% were obtained by analyzing the ^{15}N-labeled carbamazepine contained in the orally administered product.[52] This apparent discrepancy might be explained by the biliary excretion of oxidative metabolites (see below). In fact, more than half of the amount present in feces was in form of metabolites.[51,53]

Recently, an IV carbamazepine formulation was developed using β-cyclodextrin to overcome solubility problems, and the formulation was approved by the U.S. Food and Drug Administration (FDA).[54] Marino et al. infused 100 mg of this IV formulation containing ^{13}C–^{15}N-labeled carbamazepine into 92 epilepsy patients treated with oral carbamazepine products. They were able to determine carbamazepine concentrations in plasma from both formulations simultaneously through the quantification of both the label and the mass of carbamazepine (using liquid chromatography coupled to mass spectrometry, LC-MS). In that study, the absolute BA at the steady-state (BA_{ss}) was found to be 78 ± 24%, independent of patients' gender.[55] It is worth noting that Gérardin et al. labeled the orally administered carbamazepine,[52] while Marino et al. labeled the IV drug.[55] This implies that BA determined by Gérardin et al. accounted for both the parent drug and metabolites, whereas Marino et al. accounted only for the parent carbamazepine from the orally administered dose, as this was quantified by LC-MS.

In another study, Tolbert et al. switched the treatment of epilepsy patients from their typical oral carbamazepine to an IV infusion, whose dose corresponded to 70% of their total oral daily dose.[56] By comparing the area under the plasma concentration-time curve (AUC) from the IV infusion and oral administration, authors observed that these values fell within the 90% confidence interval (CI) regardless of the infusion time. Moreover, the 30 min IV infusion was bioequivalent with the oral product in both AUC and maximum plasma concentration (C_{max}),[56] consistent with the BA of 78% reported by Marino et al.[55] Taken together, the literature suggests that the incomplete BA of carbamazepine (70–78%) might be principally related to first pass metabolism (see section Distribution, metabolism and excretion) rather than incomplete absorption.

The range of AUC values after oral administration of carbamazepine 200 mg IR tablets is around 120–190 μg*h/mL.[57,58] These values proportionally rise to 240–300 μg*h/mL when 400 mg are administered, suggesting linear pharmacokinetics within this dose range.[26] Linearity was further demonstrated over the range 50–600 mg.[59,60] Even though a slight disproportion was detected at lower doses (i.e. 50 and 100 mg),[58] this was almost negligible and may be attributable to nonlinear hepatic metabolism rather than nonlinear absorption.

The C_{max}, which is indirectly related to the absorption rate, seems to be more variable than AUC. For instance, values from 1.15 to 2.70 μg/mL were reported after the administration of 200 mg IR tablets to healthy subjects.[61,62] Nonetheless, the administration of two tablets of 200 mg caused the expected proportional increase in C_{max} (3.20–5.90 μg/mL). The absorption of oral solutions was faster than that of suspensions, which in turn was faster than for tablets.[60,63] This suggests that the *in vivo* performance of carbamazepine is to some extent dependent on the dosage form, and for solid dosage forms, potentially on the disintegration step and particle size.[63] Food also seems to have a modest influence carbamazepine absorption, since concomitant meal intake caused an increase of 20 and 25% in the AUC and C_{max}, respectively, although the effect was only statistically significant for C_{max}.[60]

Carbamazepine is slowly absorbed, showing a plasma peak at 24 h (T_{max}).[16,59] However, this value widely varied between 1.5 and 32 h (for the reference product), or 1–48 h (for many other IR formulations).[26] Carbamazepine's plasma-time curves display a plateau-like form when maximum concentrations were reached, in which several minor plasma peaks were identified.[26,60] This would be the most likely explanation for the above-mentioned erratic variation in T_{max}. This variation is perhaps amplified by carbamazepine's relatively long elimination half-life. Interestingly, this plateau-like behavior was not seen when carbamazepine was administered as an alcoholic oral solution,[58] suggesting that variability in C_{max} and T_{max} might be consequence of a limiting dissolution rate and a similarly rapid permeability along the gastrointestinal tract.

Permeability

Table 2 shows carbamazepine permeability values measured using a variety of experimental approaches.[64–71] Caco-2 and human permeability values were within the range of 10^{-5} to 10^{-4} cm/s, respectively. In both cases, carbamazepine permeabilities were higher than those of metoprolol, a high permeability reference compound.[64,71] Inter-study differences could be explained by different concentrations used, cell densities, presence or absence of collagen on *in vitro* membrane, and calculation methods, among other variables. Efflux ratio (ER) values were consistently reported as 0.78 to 1.27, regardless of the experimental set-up. Furthermore, the presence of verapamil, a well-known P-glycoprotein (P-gp) inhibitor, did not alter either carbamazepine permeability or its ER.[68] The absence of P-gp mediated transport was further confirmed by *in vitro* studies in seven different cell models, including over-expression systems.[72,73] Carbamazepine transport by breast cancer resistance protein (BCRP) was also assessed across transfected monolayers, where no differences between absorptive and secretory transport were found.[74] Overall, the evidence obtained with different *in vitro* experimental models agrees with both the high permeability and linear pharmacokinetics observed *in vivo*.

Table 2
In Vitro and *In Vivo* Permeability Data of Carbamazepine.

Method	Concentration (μM)	$P_{app,\ A\text{-}B}$ (cm/s,10^{-5})	ER	Ref
Caco-2	10	N.R.	0.78	69
	10–300	6.2	0.90	64
	25	14.4	0.84	67
	100	5.0	1.27	65
	1000	2.7	1.27	65
	N.R.	20.9	N.R.	70
PAMPA	100–200	1.2	N.R.	68
		$P_{app,\ M\text{-}S}$		
Mice intestine Ussing Chamber	200	1.5[a]	0.93	66
	+ Verapamil 200 μM	1.4[a]	1.03	66
Human intestinal double-balloon		P_{eff} (cm/s,10^{-4})		
	N.R.	4.3		71

$P_{app,\ A\text{-}B}$, Apparent permeability in the apical-to-basolateral (absorptive) direction; $P_{app,\ M\text{-}S}$, Apparent permeability in the mucosa-to-serosa (absorptive) direction; P_{eff}, Effective permeability; ER, Efflux ratio calculated by dividing basolateral-to-apical apparent permeability ($P_{app,\ B\text{-}A}$) by $P_{app,\ A\text{-}B}$; N.R, Not reported.

Distribution, Metabolism and Excretion

Carbamazepine is widely distributed throughout the body. The plasma protein binding is approximately 75%, with slight inter-individual variation.[58] The apparent volume of distribution (Vd) ranged from 0.79 to 1.86 L/kg,[58,75] and it was found to be highly affected by other drugs.[58] Consistent with its lipophilicity and permeability, carbamazepine is also distributed into breast milk and able to cross the placental barrier.[59]

After oral administration of a single dose, carbamazepine plasma elimination half-life ($t_{1/2}$) was relatively long, around 34–38 h,[58] with approx. 75% of the dose being excreted with the urine. From this fraction, only 2% was eliminated as the parent drug.[16,59] Metabolism, therefore, plays an important role in carbamazepine elimination. Its only active metabolite is carbamazepine-10,11-epoxide, which is formed by the action of diverse isoforms of cytochrome P450 (e.g. 3A4 and 2C8).[76–78] The effect of the CYP 3A4 inhibitor, grapefruit juice, on carbamazepine pharmacokinetics was studied in 10 patients treated with oral carbamazepine by following the $AUC_{0\text{-}8}$, the minimum ($C_{min,ss}$) and the maximum ($C_{max,ss}$) steady-state concentrations. The authors found that the aforementioned parameters increased by 40.8, 39.2 and 40.4% respectively in patients who received carbamazepine co-administered with grapefruit juice. Considering the strong intestinal expression of CYP 3A4 and the interaction with grapefruit juice, the occurrence of first pass metabolism in the intestinal wall is plausible.[76] Drug-food interactions have also been reported in various research publications and study cases.[79–81] Therefore, the first pass extraction appears to be the main explanation for the reported absolute BA of between 70 and 78%.[55]

The epoxide metabolite is finally biotransformed into the *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (*trans*-CBZ-diol), which is excreted by the kidney (21% of the dose).[16] However, since carbamazepine can induce its own metabolism,[16] this value may be even larger in chronically treated patients. Moreover, co-administration with inducers of drug metabolism, such as phenytoin, might have an even greater impact. For example, Eichelbaum et al. demonstrated that carbamazepine elimination half-life decreased to 12 h in patients receiving chronic treatment and to 8 h in patients co-medicated with phenytoin.[16,75]

Dosage Form Performance

Bioavailability and Bioequivalence

Several studies on carbamazepine comparative BA and BE for oral IR dosage forms were found in the literature (Table 3). Further, reports that contained both *in vitro* and *in vivo* comparative studies and correlations are shown in Table 4. The pharmacokinetic parameters for the reference product (usually Tegretol®) containing carbamazepine 200 mg were consistent between single dose studies, with AUC and C_{max} values lying in the range from 144 to 182 μg*h/mL and from 1.89 to 2.43 μg/mL, respectively. These ranges remained similarly narrow when two 200 mg IR Tegretol® tablets (400 mg of carbamazepine in total) were administered to volunteers (Tables 3 and 4).[26,43,50,82] By contrast, test (generic) products often showed wider variability than the reference. Although BE was demonstrated for some generic products, some other test formulations failed the BE test mainly due to the C_{max} parameter (Tables 3 and 4).

The statistical criteria applied to reach a BE decision varied among studies. While typical statistical tests such as the paired *t*-test and ANOVA were performed in studies conducted between 1979 and 1995,[57,83] the confidence intervals were calculated in more recent publications (Tables 3 and 4). Of note, two studies used an innovative parameter ('A') which depended on the absorption constant (K_a), elimination constant (K_e), mean residence time (MRT), t_{max} and $AUC_{0\text{-}inf}$.[84,85] Although the 'A' parameter was advantageous improving the accuracy of relative bioavailability calculations for two generic products,[84] it seems difficult to fully rely on it because of the dependency on modeling required to estimate kinetic rate constants.

Often, concerns arise around demonstration of BE for NTI drugs, such that further evidence (i.e. multiple dose studies) could be requested. Three studies containing both single dose and multiple dose comparative data were located.[25,57,86] Anttila et al. studied the bioequivalence of one carbamazepine brand against the reference product in either subjects (single dose) or patients (multiple doses). Even though the C_{max} obtained with the test product after the single dose experiment was significantly higher than the reference, there were no statistical differences between C_{ss} in patients.[57] Similarly, Yacobi et al. showed that the $C_{max,ss}$ and AUC from the generic product were indistinct from the reference in a multiple dose study conducted in healthy volunteers, even using the 90% CI limits: 0.9–1.1. The same formulation had not been declared BE in a previous single dose study because of the AUC parameter.[25] These findings support the sensitivity of the single dose experimental design to detect differences in the pharmacokinetic performance of two pharmaceutical alternatives, although steady state data are more representative of the actual clinical use of the drug.

Is There a Polymorphism Effect on BA?

Since diverse polymorphic forms are reported in the literature (see *physicochemical properties*), it is worthwhile to address their potential effect on carbamazepine oral performance. Anhydrous carbamazepine is converted into DH in aqueous solution such that

Table 3
Summary of Published Bioequivalence Studies on Carbamazepine Immediate Release Tablets in Fasted Humans.

Subjects (nº Females; Males)	Study Design	Drug Product (Manufacturer)	Dose (mg)	AUC (μg[e]h/mL)	C_{max} (μg/mL)	Criteria and Result	Ref
9 healthy volunteers (4; 5)	Single dose, two-period, crossover.	Tegretol® (Ciba Geigy Pharm)[d]	200	182[a]	2.43	Paired *t*-test. Not BEs (C_{max}, $p < 0.001$).	57
		Neurotol® (Lääke/Farmos Group)	200	190[a]	3.40		
12 healthy volunteers (0; 12)	Single dose, two-period, crossover, randomized.	Tegretol® (Novartis India Limited)[d]	200	129[b]	2.17	Paired *t*-test. Not BEs (C_{max} and 'A' parameter, see below).	85
		Zen	200	150[b]	3.10		
5 healthy volunteers (0; 5)	Single dose, three-period, crossover, randomized.	Tegretol[d]	200	145[a]	2.11	'A' parameter (function of: Ka, Ke, MRT, t_{max} and AUC). BEs.	84
		Temporol[e]	200	162[a]	2.49		
		Karazepin[e]	200	127[a]	1.71		
9 healthy volunteers	Single dose, two-period, crossover, randomized.	Tegretol®[d]	400	272[b]	5.61	ANOVA. BEs.	83
		Marzepine (ICN Galenika)[e]	400	260[b]	4.29		
6 patients (2; 4)	Multiple doses, two-period, crossover.	Tegretol® (Ciba Geigy Pharm)[d]	PDNA	NR	NR	Paired *t*-test on mean concentrations. BEs	57
		Neurotol® (Lääke/Farmos Group)[e]	PDNA	NR	NR		
18 epilepsy patients.	Multiple doses, Three-period (three weeks/period), crossover, double-blind, randomized, non-washout.	Tegretol (Ciba Geigy Pharm)[d]	PDNA	85.6	11.0	MANOVA and IC 90% (0.8−1.25). BEs, except Panital (AUC).	86
		Carmapine (Central-Poly)[e]		85.0	10.5		
		Carzepine (Condrugs)[e]		93.0	11.0		
		Panital (Pharmaland)		98.2	10.5		
32 healthy volunteers (0; 32)	Multiple doses, Two-period (11 days/period), crossover, fasted, open-label, randomized, non-washout.	Tegretol (Ciba Geigy Corp.)[d]	200 t.i.d.	153	7.10	ANOVA, IC 90% and IC 95% (0.9 −1.1). BEs	25
		Test (Taro Pharm. Ind. Ltd)[e]	200 t.i.d	156	7.11		
40 patients either seizure-free or with refractory seizures	Multiple doses, Two-period (90 days/period), crossover, double blind, randomized, non-washout.	Tegretol (Ciba Geigy Corp.)[d]	PDNA	0.61−1.87[c]	6.2−16.0	Paired *t*-test on AUC. BEs	104
		Epitol (Lemmon Co.)[e]	PDNA		6.7−15.9		
12 young (6.5−15 yo) seizure patients (3; 9)	Multiple doses, two-periods (six weeks/period), crossover, non-washout.	Tegretol (Ciba Geigy Corp.)[d]	100 or 200 (PDNA)	98.9	10.2	Paired *t*-test. BEs	105
		Test (Ethical Generics)[e]		97.4	9.91		

BEs, Bioequivalents; PDNA, Patient's dose not adjusted; NR, Not reported.
[a] $AUC_{0\text{-}inf}$.
[b] $AUC_{0\text{-}t}$.
[c] Minimum and maximum values for intra-patient AUC ratios.
[d] Reference Product.
[e] Bioequivalent formulation.

Table 4
Summary of Further Single Dose Bioequivalence Studies and Dissolution Conditions Attempting IVIVC for Carbamazepine Immediate Release Products.

Drug Product Manufacterer	Dose (mg)	$AUC_{0\text{-}inf}$ ($\mu g^{b}h/mL$)	C_{max} ($\mu g/mL$)	*In-Vitro* Method Used in the Correlation	Correlated Parameters	Other Significant Results	Ref
Ciba Geigy Pharmaceuticals.[a]	200	144	1.89	➢ Media: 900 mL SLS 1%.	➢ Fa vs Fd (30–90 min).		61
Pharmaceutical Basics: Batch 1[b]		80.9	1.15	➢ Apparatus: Paddle.	➢ $AUC_{0\text{-}inf}$ or C_{max} vs Fd (15–60 min)		
Pharmaceutical Basics: Batch 2[b]		154	2.69	➢ Speed: 75 rpm.			
Pharmaceutical Basics: Batch 3[b]		105	1.40				
Ciba Geigy Pharmaceuticals.[a]	200	157	1.95	➢ Media: 900 mL SLS 1%.	➢ Fa vs Fd (30–120 min).		102
Inwood		163	2.32	➢ Apparatus: Paddle.	➢ C_{max} or T_{max} vs Fd (5–30 min).		
Sidmak		159	2.30	➢ Speed: 75 rpm.			
Purepac[b]		163	2.34				
Formulation A	200	–	1.90	➢ Media: 900 mL SLS 1%.	➢ Correlation parameters obtained from *in vitro* and *in vivo* data from three formulations.	Plasma profile of the remaining formulation predicted from correlation parameters.	62
Formulation B		–	2.70	➢ Apparatus: Paddle.			
Formulation C		–	2.30	➢ Speed: 75 rpm.			
Formulation D		–	2.50				
Ciba Geigy Pharmaceuticals.[a]	400	296	4.24	➢ Media: 900 mL simulated USP intestinal fluid, pH = 7.5.	➢ AUC vs Fd (45–90 min)	Neither SLS 1% nor HCl 1 N datacorrelated with *in vivo* parameters.	97
Amstrong[b]		331[c]	5.98				
Wayne[b]		316[c]	4.81	➢ Apparatus: Paddle.			
Precimex[b]		368[c]	5.98	➢ Speed: 75 rpm.			
Ciba Geigy Pharmaceuticals.[a]	400	296	4.54	➢ Media: 900 mL SLS 1% or HCl 1 N.	➢ C_{max} vs $Fd_{1\%\ SLS}$ (20–100 min).	Correlations were also obtained with HCl 1 N, although worse than with SLS.	26,43
Pharmachemie[b]		246	3.29	➢ Apparatus: Paddle.			
Centrafarm[b]		294	5.90	➢ Speed: 75 rpm.			
Pharbita[b]		292	6.15				
Reference product	400	211	4.34	➢ Media: 900 mL water, SLS 0.5, SLS 1%, HCl 0.1 N, USP Acetate (pH 4.5), USP phosphate (pH 6.8).	➢ Fa vs Fd point to point (Level A)	Overall, acceptable correlations being SLS 1% the highest r.[2]	106
Galenika a.d.[b]	400	220	4.74	➢ Apparatus: Paddle.			
				➢ Speed: 75 rpm.			
Novartis.[a]	400	259	4.74	➢ Media: 900 mL SLS 0.5 or 1%.	➢ Plasma profile predicted from *in vitro* data and *in silico* modeling.	Dissolution in USP buffer 4.5, 6.8 and HCl 0.1 N were not consistent with *in vivo* results.	50
Formulation Test.	400	259	4.34	➢ Apparatus: Paddle.			
				➢ Speed: 75 rpm.			
Novartis (Bioeq. Study 1).[a]	400	238	3.20	➢ Media: 900 mL SLS 1%.	➢ *In vitro* vs *in vivo* dissolution time		82
Formulation Test 1		238	3.40	➢ Apparatus: Paddle.	➢ Fa vs Fd point to point (Level A).		
Novartis (Bioeq. Study 2).[a]		243	3.20	➢ Speed: 75 rpm.			
Formulation Test 2[b]		230	2.90				
Novartis[a]	400	355	4.00	➢ Media: 900 mL water; 1% SLS.	➢ *In vitro* vs *in vivo* dissolution time		103
Test Formulation	400	389	5.14	➢ Apparatus: II.	➢ Fa vs Fd point to point (Level A).		
				➢ Speed: 75 rpm.			

Fd, Fraction dissolved; Fa, Fraction absorbed.
[a] Reference Product.
[b] Bioequivalent formulation.
[c] $AUC_{0\text{-}120}$.

the crystallization of this latter form seems to be the kinetic rate-limiting step in dissolution when the concentration exceeds the thermodynamic solubility. Nonetheless, after grinding the solid material, a decrease in the interconversion times was observed. This was associated with a change in the rate-limiting step to the dissolution of the anhydrous form.[37] All in all, it can be expected that the DH is the most prevalent form in suspensions because of the solution-mediated transformation. Further, the conversion rates of diverse forms of carbamazepine have been reported. Typically, faster conversion of Form I into DH was demonstrated, in comparison with Form III.[34,35,87] The intrinsic dissolution rate (IDR) of Form III was only slightly faster than Form I, less than 1.1-fold higher.[34,36,87] Most of the studies, however, agreed that anhydrous polymorphs dissolved between 1.6- and 2.3-fold faster than the less soluble DH carbamazepine.[34,36,87,88] Conversely, one report showed that amorphous dissolution was slower than the DH in a flow-through apparatus, using HCl 0.1 N as media. In this report, the authors also observed an increment in dissolution rate of the anhydrous form in presence of the wetting agent polysorbate 80. The enhanced dissolution rate was accompanied by a decrease in the crystal length, hence their findings were explained in the light of the anhydrous form having a higher tendency to crystal growth in HCl media.[89]

The presence and effect of polymorphs were studied in four marketed products. The IDR of products in which Forms I and III prevailed displayed the fastest IDR, although the differences were negligible compared to the slowest of those drug products (<1.15-fold). Meanwhile, the formulation that contained carbamazepine Form IV showed an IDR 1.8-fold slower than the fastest drug product.[38]

The oral performance of diverse polymorphs was studied in dogs, where the BA of Form III, I and DH in dogs were 69, 48 and 33%, respectively, compared to the oral solution. These results likewise indicate that the BA of Form III was 1.4 or 2.1-fold greater than Form I or DH, respectively.[34] Given that this behavior was not reflected in the *in vitro* dissolution experiment, the authors suggested that discrepancies might be due to disparities in rates of conversion.[34,35,87] Yet, the situation in humans is dissimilar. In this regard, Kahela et al. administered 200 mg of either anhydrous carbamazepine or DH in hard gelatin capsules to healthy volunteers. The *in vitro* dissolution results differed between the two formulations, but no differences were found in AUC and C_{max} parameters.[89] Likewise, Elqidra et al. prepared IR tablets containing 200 mg of different carbamazepine polymorphs, which were compared to the reference product, Tegretol®. The authors found that AUC and C_{max} values of drug product 1 (containing Form I), 2 (containing bulk carbamazepine), and 3 (the reference) were statistically insignificantly different from another.[90]

Excipients and Manufacturing Effects on BA

Table 5 displays the excipients present in IR carbamazepine 200 mg tablets with a market authorization (MA) in diverse countries. Besides carbamazepine 200 mg tablets, some companies

Table 5
Excipients Present in Carbamazepine IR Tablets 200 mg with Marketing Authorization (MA) in Diverse ICH and Associated Countries and the Minimal and Maximal Excipient Amount Present per Dosage Unit in Solid Oral Drug Products with MA in US.

Excipient	Drug Products[a], by Country[b] That Granted the MA[c]	Range Present in Solid Oral Dosage Form with MA in US (mg)[d]
Carmellose sodium	AU (1), CA (8), DE (12,13), ES (18), NL (23,26), UK (28), US (30)	3–160
Croscarmellose sodium	BR (3–7), DE (14,16), US (29,32,34)	9–165
Cellulose, hydroxypropyl	CN (11), JP (21,22)	0.4–198
Cellulose, ethyl	US (34)	2–292
Cellulose, methyl	NL (24)	3–184
Cellulose, microcrystalline	AU (1,2), BR (3–7), CA (8–10), DE (12–17), ES (18,19), JP (20–22), NL (25,26), UK (27,28), US (29,30)	27–1553
Silicon dioxide	AU (1,2), BR (4–6), CA (8,9), CN (11), DE (12,14–17), ES (18,19), NL (25,26), UK (27,28), US (30–34)	3–139
Gelatin	DE (13), NL (23), US (33)	2–756
Glycerin	US (33,34)	1–249
Hypromellose	JP (20), US (31)	1.2–537
Lactose	BR (5), US (34)	33–2500
Magnesium stearate	AU (1,2), BR (3–7), CA (8–10), CN (11), DE (12–17), ES (18,19), JP (20–22), NL (23–26), UK (29–34)	0.2–401
Povidone	BR (3–7), CA (10), DE (17)	0.5–240
Sodium laurylsulphate	BR (6), CA (10), DE (17)	0.3–148
Sodium starch glycolate	AU (2), CA (10), DE (15), ES (19), NL (25), UK (27), US (31,34)	2.4–876
Starch	BR (5,7), CN (11), DE (17), JP (20,21), NL (23, 24), US (31,33)	0.4–1000
Starch, hydroxypropyl	JP (22)	–
Starch, pregelatinized	AU (2), NL (24,25), UK (27), US (31,32)	32–453
Stearic acid	US (33)	5–72
Talc	AU (2), JP (21), NL (24,25), UK (27)	2–1000

[a] Manufacturers: 1: Novartis Pharmaceuticals Australia Pty Ltd.; 2: Alphapharm Pty Ltd.; 3: EMS S/A.; 4: Cristália Prod. Quím. Farm. Ltda.; 5: Brainfarma Indústria Química e Farmacêutica S.A.; 6: Laboratorio Teuto S/A.; 7: Sanval Comércio e Indústria Ltd.; 8: TARO PHARMACEUTICALS INC.; 9: NOVARTIS PHARMACEUTICALS CANADA INC.; 10: TEVA CANADA LIMITED; 11: Beijing Novartis Pharma Ltd.; 12: HEUMANN PHARMA GmbH; 13: RATIOPHARM GmbH; 14: NOVARTIS PHARMA GmbH; 15: 1 A Pharma GmbH; 16: Aristo Pharma GmbH; 17: neuraxpharm Arzneimittel GmbH; 18: Novartis Farmacéutica, S.A.; 19: Laboratorios Normon, S.A.; 20: Sun Pharma; 21: Kyowa Pharmaceutical Industry; 22: Fujinaga Pharm; 23: Apotex Europe B.V.; 24: Centrafarm B.V.; 25: Mylan B.V; 26: Novartis Pharma B.V.; 27: Mylan; 28: Novartis Pharmaceuticals UK Ltd.; 29: APOTEX INC ETOBICOKE SITE; 30: TARO PHARMACEUTICAL INDUSTRIES LTD; 31: TORRENT PHARMACEUTICALS LTD; 32: UMEDICA LABORATORIES PRIVATE LTD; 33: NOVARTIS PHARMACEUTICALS CORP; 34: TEVA PHARMACEUTICALS USA INC.

[b] Countries: AU: Australia; BR: Brazil; CA: Canada; CN: China, DE: Germany, ES: Spain, JP: Japan, NL: the Netherlands, UK: United Kingdom, US: United states.

[c] Therapeutic Goods Administration (TGA). Available at: https://www.tga.gov.au. Accessed May 05, 2020.; ANVISA (Brazilian Health Regulatory Agency). Available at: www.anvisa.gov.br Accessed May 26, 2020.; Health Canada. Available at: www.hc-sc.gc.ca. Accessed May 11, 2020.; China Food and Drug Administration (CFDA). Available at: http://en.nhc.gov.cn. Accessed May 04, 2020.; Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). Available at: https://www.pharmnet-bund.de. Accessed May 04, 2020.; Spanish Agency for Medicines and Health Products. Available at: www.aemps.es. Accessed May 11, 2020.; Pharmaceuticals and Medical Devices Agency (PMDA). Available at: https://www.pmda.go.jp/english/. Accessed May 04, 2020.; Medicines Evaluation Board. Available at: www.cbg-meb.nl. Accessed May 11, 2020.; Electronic medicines compendium. Available at: www.medicines.org.uk/emc. Accessed May 06, 2020.; National Institute of Health. US National Library of Medicine. Available at: www.dailymed.nlm.nih.gov. Accessed May 06, 2020.

[d] U.S. Food and Drug Administration. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download. Accessed August 27, 2020.

also manufacture IR tablets containing 100, 300 or 400 mg, although the qualitative composition declared is the same.

Being a poorly aqueous soluble drug, the presence of SLS in IR tablets may enhance carbamazepine's oral performance by increasing either the wettability or solubility.[44] In this monograph we found three generic products that declared SLS in their qualitative composition (Table 5). As mentioned above, carbamazepine is a highly permeable drug with almost complete absorption. Therefore, if any SLS effect will occur, this will most likely be reflected in the C_{max} parameter.

The quantitative amount of SLS in solid oral dosage forms with a MA in the United States ranges from 0.3 to 148 mg. However, the upper limit may not be representative for a 200 mg carbamazepine formulation, since this would imply an extremely high relative amount of SLS in those formulations. Considering that these three generic products were granted with a MA in their respective countries (and thus, it is very likely that bioequivalence has been previously demonstrated), we believe that SLS amounts in carbamazepine IR tablets may be near or even below the lower limit reported by the FDA's inactive ingredient database (Table 5).

Besides carbamazepine IR tablets, chewable tablets have also been developed and are currently available in the market.[29] The clinical pharmacokinetic performance of chewable relative to IR tablets was studied in adults and young populations. Chan et al. carried out a single dose, three-period, crossover study in six healthy volunteers who were administered the IR product, chewable tablets swallowed as a whole (SW) and chewable tablets chewed for 30 s before swallowing (CHW). Among these treatments, only CHW failed the BE study (95% CI, >20%) due to the C_{max} (4.19 μg/mL), which was 1.25-fold greater than the reference (3.36 μg/mL). However, the IR and CHW treatments were compared once again in a multiple doses study conducted in ten healthy volunteers, where no significant differences between C_{ss} (4.9–5.0 μg/mL) were found.[91] Likewise, another multiple dose, two-period, crossover study conducted in young epileptic patients (6–14 yr) displayed that $C_{max,ss}$, C_{ss} and AUC were not different between the IR and the chewable product.[92] In that study no information was given about whether the chewable tablets were swallowed as a whole or chewed.

The effect of particle size on BA has also been investigated. Dam et al. measured carbamazepine plasma profiles in epileptic patients after the administration of two tablets manufactured with either small (test product, in average 2–3 μm) or large (reference product, in average 100–150 μm) particle sizes. The authors found that C_{max} of the carbamazepine product with the large particle size was just 75% of that of the product with the small particle size.[93] Therefore, it is plausible that discrepancies in particle sizes could explain outcomes in some studies that have been unable to demonstrate BE.

Dissolution and IVIVC

Dissolution conditions for carbamazepine according to the U.S. Pharmacopeia (USP) 42nd edition are 900 mL of water containing 1% of sodium laurylsulfate (SLS 1%) as the dissolution medium, in USP type II apparatus (paddle) at a rotational speed of 75 rpm.[10,94] However, the specifications depend on the product. Pharmacopeial Test 1 applies only to 100 mg chewable tablets and is thus out of the scope of this manuscript. For IR tablets two different specifications are listed: Test 2: 45–75% of drug dissolved within 15 min, and no less than 75% after 60 min; or Test 3: 60–85% of drug dissolved within 15 min, and no less than 75% after 60 min.

Mittapalli et al. studied six IR marketed drug products containing 200 mg of carbamazepine tablets under different conditions. All six formulations met USP criteria when the USP conditions were applied, however the SLS-containing media were not able to distinguish among formulations.[45] Instead, the authors obtained more discriminating dissolution profiles when experiments were carried out in SLS-free HCl 0.1 N media. However, the clinical relevance of these findings is unclear because no *in vivo* data were reported.[45] Using the USP type IV apparatus, Medina et al. were able to discriminate better between five different marketed drug products than was possible with the USP monograph method.[95] Here too, the lack of *in vivo* data makes it impossible to draw conclusions about the biorelevance of the results.

Overall, Table 4 shows that USP dissolution conditions resulted in the best biorelevance for carbamazepine IR tablets. Nine out of ten studies achieved good correlations and/or predictions of plasma-time profiles from *in vitro* dissolution data using the pharmacopeial conditions. Replacing SLS by an acidic medium (HCl 1 N) also displayed good correlation,[43,96] but did not show superiority over the SLS 1% medium.[43] Examples for successful correlations obtained with SLS 1% are shown in Fig. 2. The performance of different SLS concentrations has also been assessed where one report showed that SLS 0.5% enabled successful prediction of plasma-time profiles,[50] while other work displayed the best predictions with SLS 0.1%.[63] Conversely, only one study reported that neither SLS nor HCl media correlated well with AUC parameter.[97]

The results from the literature agree that best correlations were obtained when using fraction dissolved (Fd) within 30–90 min. However, the choice of the *in vivo* parameter for establishing the correlation (Fa, AUC, C_{max}) was diverse, as shown in Fig. 2 and Table 4. Of note, some good correlations were also found with Fd at 5 min, although this might be irrelevant as this timeframe is shorter than the gastric emptying time (around 15 min).[43]

Discussion

Solubility

The highest strength of carbamazepine as an IR solid dosage recommended in the EML is 200 mg. Regulatory FDA guidance recommend the use of USP buffers within the pH range 1.2–6.8 (chloride, acetate or phosphate) to assess drug solubility.[7] However other buffers can be used whenever justified.[1,6] Considering the lack of physiologically relevant ionization, carbamazepine's solubility should not be dependent on the type of buffer. Table 1 shows that carbamazepine solubility was insensitive to pH and any other biorelevant content (i.e. bile components present in simulated media). Table 1 also reports D/S ratio values, which reflect the volume of medium needed to dissolve the respective dose strength. The D/S ratio ranged from 588 to 849 mL, respectively and thus is 2.4- to 3.4-fold higher than the cut off volume of 250 mL stipulated by the regulators.[7] Consistently, Amidon et al. reported a D/S ratio of 769 mL, implying that a dose number (Do) of around 3 can be obtained for a dose of 200 mg.[39] This number is even greater when the highest recommended single clinical dose, 400 mg, is considered, as required by the regulatory guidances.[2,6] Therefore, carbamazepine can be unequivocally classified as a “not highly soluble” drug according to the BCS.

Permeability

Different methodologies can be used to assess drug permeability. An API is considered highly permeable if the extent of its absorption (using the Fa parameter) is equal or higher than 85%, provided its stability in the gastrointestinal tract. The guidances recommend conducting either mass balance in humans or absolute BA experiments as a first preference to classify the API permeability. In the literature, both mass balance and BA studies are available and these consistently suggest that oral carbamazepine bioavailability is around 70–80%.[51–53,55] However, it is very likely that this range

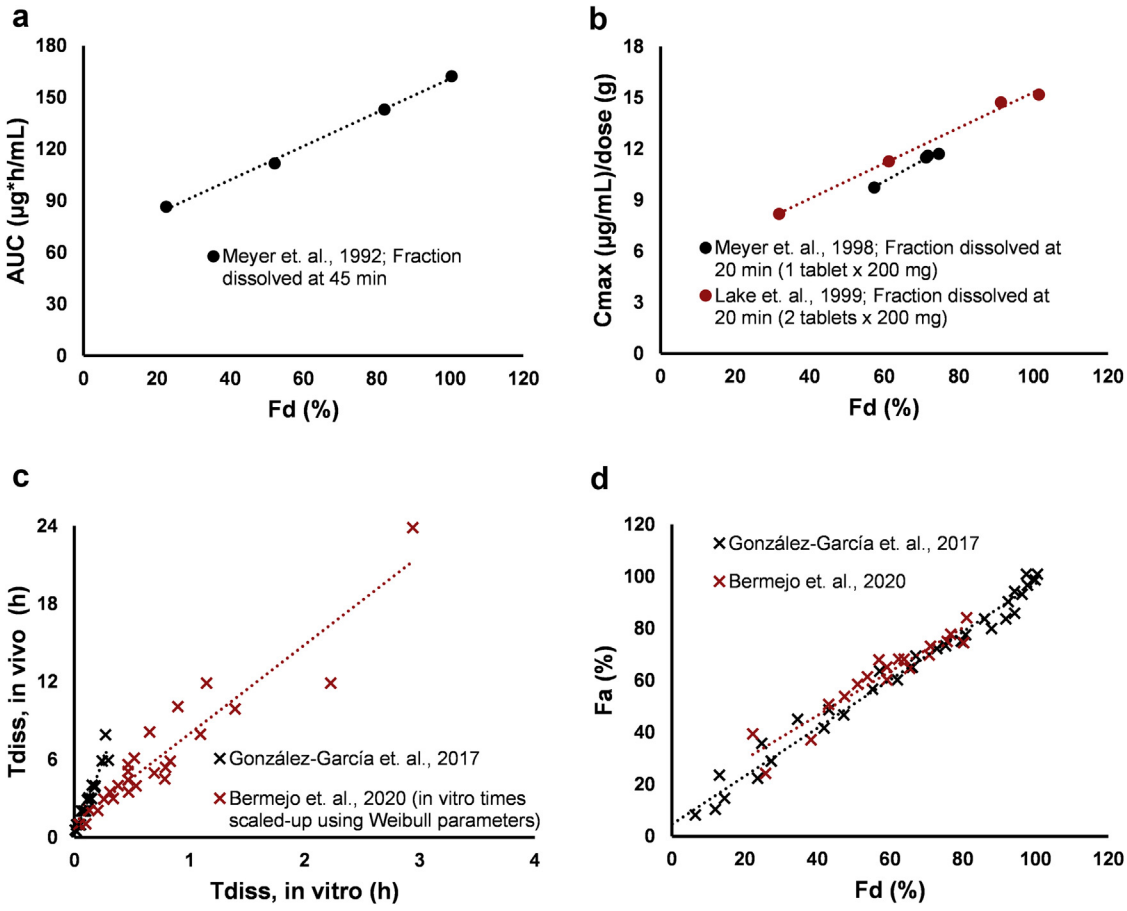

Fig. 2. Examples of level C (upper panels, circles) and level A (lower panels, crosses) IVIVC found in literature using 900 mL of SLS 1% in the USP type II apparatus at 75 rpm. Data was digitalized from Ref.[61] (a),[43,102] (b),[82,103] (c and d) with PlotDigitalizer 2.6.8 (Free Software Foundation, Inc., Boston, MA). C_{max} values in panel B were normalized by carbamazepine's dose utilized in each study (g) in order to allow data comparison. Differences between correlations in panel C may be consequence of the scaling step carried out in Bermejo and coauthors' study (red crosses).

underestimates the true absorption, as the first pass extraction seems to play an important role in carbamazepine oral disposition. In fact, the oral BA of carbamazepine in patients increased by 40% when it was co-administered with grapefruit juice (which contains CYP3A4 inhibitors) compared to co-administration with water.[76]

The BCS framework was developed using human permeability data obtained with intestinal perfusion techniques which allow direct permeability assessment. The effective permeability of carbamazepine was measured as 4.3×10^{-4} cm/s, 3.3-fold larger than the high permeability marker, metoprolol.[71] Such a study provides confirmatory evidence to classify carbamazepine as a highly permeable drug. Consistently, several surrogate *in vitro* experiments shown in Table 2 point toward the same conclusion. The FDA and the recently published ICH M9 guidances permit the use of *in vitro* Caco-2 cell experiments as a surrogate method to assess drug permeability.[7,8] Therefore, the good agreement between *in vivo* and *in vitro* observations published in the literature on carbamazepine provides additional support for the regulatory decision of including cell monolayer experiments as a surrogate tool for permeability evaluation.

The classification of carbamazepine as "highly permeable" is also in line with its molecular structure (Fig. 1) and reported LogP values. Indeed, carbamazepine is currently listed in both guidances as a high permeability model drug.[7,8] Moreover, *in vivo* linearity within the dose range 50–600 mg was demonstrated,[59,60] and supported by *in vitro* bidirectional studies in presence or absence of inhibitors that confirmed the null role of intestinal transporters (i.e. P-gp and BCRP).

BCS Classification

In 1995, Amidon et al. used carbamazepine as an example of a low solubility API (Do = 3).[39] Thereafter, many publications supported its classification as a BCS class 2.[42,98–100] For instance, Kasim et al. classified the drugs in the WHO list of essential medicines according to the BCS framework. The authors used LogP values indirectly accounting for permeability, which resulted in a Class 2 classification.[42] However, regulatory guidances do not consider descriptors of lipophilicity (i.e. LogP, LogD) in assessing drug permeability.[1,6,7] Regarding the evidence found, data from both *in vivo* and *in vitro* experiments lead to high permeability classification. Indeed, the FDA guidance lists carbamazepine as a model drug of high permeability.[7] Furthermore, the several examples of successfully achieved IVIVC demonstrate that carbamazepine dissolution, and not the permeation, would be the rate limiting step in its oral absorption.[43,50,62,63,82,96] Considering the whole body of evidence collected, carbamazepine can be classified as a BCS Class 2 drug.

Surrogate Techniques for In Vivo *BE Testing*

Given that carbamazepine dissolution appears to control carbamazepine absorption rate from IR products, a dissolution test may be an appropriate surrogate assay and thus a valuable tool for predicting the outcome of a BE study. This would be meaningful only if a high probability of detecting bioinequivalence by this method is demonstrated.[101]

IVIVCs were achieved in two studies that used SLS-free media: HCl 0.1 N and Simulated USP intestinal fluid at pH 7.5, respectively. However, the potential of using SLS-free buffers remains controversial. For instance, the absence of relevant pKa led to assume that the pH would not play a significant role in dissolution and solubility. Actually, water, as well as other aqueous buffers in the pH range 1.2−6.8, were unable to discriminate between bioinequivalent formulations.[50] In contrast, SLS not only increased the solubility of carbamazepine (Table 1), but also its dissolution,[44,46] suggesting a need to assess the concentration of SLS in the dissolution media. In this regard, several reports of successful IVIVC found in the literature endorse the use of SLS 1% as a suitable dissolution media for IR solid oral products containing carbamazepine.[26,43,50,61,62,82,102] As shown in Table 4, the USP conditions (900 mL SLS 1%, apparatus II, 75 rpm) appears to be sufficiently discriminating in terms of detecting a failure to meet bioequivalence. Nine out of the ten studies found in the literature achieved successful IVIVCs by using the USP conditions.[26,43,50,61,62,82,102] These data strongly support the application of this method as a surrogate technique. It is plausible that the usefulness of SLS 1% as *in vitro* dissolution media relies on the high carbamazepine solubility in this media (Table 1), which provides an improved sink for carbamazepine similar to the one *in vivo* cause by its high intestinal permeability (Table 2). Lastly, although certain changes in the dissolution media and apparatus have been proposed to detect some differences that the USP method did not pick up (see section *Dissolution and IVIVC*), these approaches have not been verified with *in vivo* data yet.

In summary, pharmacopeial dissolution conditions appear to be useful not only for quality control purposes, but also a promising way forward to establishing meaningful IVIVCs for solid oral IR dosage forms containing carbamazepine. The most appropriate absorption parameters (AUC, C_{max}, Fa) to correlate against Fd over the dissolution timeframe of 5−100 min are still to be standardized. Thus, a generally applicable method with regulatory impact does not exist yet. Therefore, further definition of the parameters to be used for establishing meaningful correlations would be necessary before enabling the USP method to function as an *in vitro* surrogate technique for BE studies.

Risk of Bioinequivalence Caused by Excipients and/or Manufacturing

The risk of bioinequivalence of oral solid IR dosage forms has been reported to be intrinsically high for BCS class 2 drug products, due to their physicochemical properties, as well as the formulation and its solubilization principles. Given the existence of diverse carbamazepine forms, the potential influence of polymorphism in the clinical performance becomes an attractive topic for research. The most prevalent polymorphs in tablets were forms I and III, which are transformed into DH in aqueous solution (form I faster than III).[38] Nevertheless, the actual implications of this interconversion in the carbamazepine oral performance are still not clear.

As member of the BCS class 2 group, excipients modifying carbamazepine solubility and dissolution (i.e. surfactants) would be of concern. The risk of a false positive BE decision would remain high as long as the discrimination capacity of the applied test is poor. Diverse excipients, including SLS, were found in carbamazepine IR tablets with a MA (Table 5). However, there is still uncertainty regarding the excipient amounts and processes involved in the manufacture of those products. In one of the aforementioned IVIVC studies, the USP test was discriminating enough to establish a proper IVIVC even though the qualitative composition of the bioinequivalent formulations was different.[43] This example provides evidence of the ability of the USP method to assess the risk of inequivalence due to differences in excipients and/or manufacturing processes. Meanwhile, the substantial evidence of carbamazepine formulations failing to meet BE requirements (Tables 3 and 4) suggests that the risk of a carbamazepine product to fail bioequivalence testing is high.

Patient's Risks Associated with Bioinequivalence

Regulators have the responsibility of approving generic drug products based on evidence of BE. Therefore, the risk of a failure detecting bioinequivalence merits to be assessed also in terms of efficacy and safety. Hence, the approval of a non-bioequivalent product could negatively impact not only the efficacy of treatment, but also the patient's safety. This risk should thus be deemed as high.

Conventional *in vivo* BE studies are usually conducted on a single dose manner; thus, it could be argued that this experiment might overestimate the actual clinical relevance of the formulation tested applying such a study design. Yet, the fact that carbamazepine is an NTI compound supports its classification as presenting a high risk for the BCS-Biowaiver approach to bioequivalence.

Conclusions

Various carbamazepine polymorphs and hydrates have been reported; however, they appear to have a negligible impact on the *in vivo* performance in humans. Carbamazepine displays a pH-independent poor aqueous solubility at the highest strength/clinical doses. Additionally, even though the extent of absorption does not seem to meet the guidance requirements for high permeable drugs, it is very likely that this was caused by the first pass effect rather than poor drug dissolution/permeability. Direct permeability measurements in *in vivo* and various *in vitro* models support this conclusion. In consequence, carbamazepine can be classified as a BCS class 2 drug. Further, the overlapping therapeutic and toxic plasma concentrations lead us to consider carbamazepine as a NTI drug. Taken together, both the BCS and NTI classification suggest that a biowaiver of the *in vivo* BE test is not recommended for carbamazepine IR drug products according to current regulatory guidances.

Nevertheless, several successful examples of IVIVC agreed that the USP dissolution conditions (900 mL water 1% SLS, apparatus II and 75 rpm) were sufficiently discriminative between bioinequivalent products. Further research on choosing the adequate correlation parameters, stressing test sensitivity and defining acceptance ranges, as well as risk assessment on efficacy and safety, is needed to determine whether the *in vitro* USP method can provide a surrogate technique for *in vivo* BE studies. Currently however, a biowaiver for carbamazepine cannot be recommended and the bioequivalence of immediate solid oral dosage forms of carbamazepine should be assessed in an appropriately designed clinical pharmacokinetic study.

Aknowledgments

MAG received financial support from the Agencia Nacional de Investigación y Desarrollo (ANID), Becas de doctorado en el extranjero, nº 72180466. The contributions of Dirk Barends to this manuscript are gratefully acknowledged.

References

1. WHO. *World Health Organization, WHO Technical Report Series, No 937. Annex 8. Proposal to Waive In Vivo Bioequivalence Requirements for WHO Model List of Essential Medicines Immediate-Release, Solid Oral Dosage Forms*. World Health Organization; 2006. http://apps.who.int/medicinedocs/documents/s19640en/s19640en.pdf. Accessed August 5, 2018.

2. WHO. *21st Edition World Health Organization. WHO Model List of Essential Medicines*. twentieth ed. World Health Organization; 2019. https://www.who.int/medicines/publications/essentialmedicines/en. Accessed August 5, 2018.
3. WHO. *7th Edition World Health Organization. WHO Model List of Essential Medicines for Children*. twentieth ed. World Health Organization; 2019. https://www.who.int/medicines/publications/essentialmedicines/en. Accessed August 5, 2018.
4. Vogelpoel H, Welink J, Amidon GL, et al. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. *J Pharm Sci*. 2004;93(8):1945-1956.
5. FIP. International pharmaceutical Federation. Biopharmaceutics classification system (BCS). http://www.fip.org/bcs_monographs; 2009. Accessed January 24, 2019.
6. EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on the Investigation of Bioequivalence*. London, UK: European Medicines Agency; 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed November 27, 2019.
7. FDA. *Food and Drug Administration, U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). Guidance for Industry. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage forms Based on a Biopharmaceutics Classification System*. MD, USA: Food and Drug Administration; 2017. https://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf. Accessed November 27, 2019.
8. ICH. *International Council for Harmonization. Committee for Medicinal Products for Human Use (CHMP). ICH M9 Guideline on Biopharmaceutics Classification System-Based Biowaivers, Setp 5*. Amsterdam, The Netherlands: European Medicines Agency; 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m9-biopharmaceutics-classification-system-based-biowaivers-step-5_en.pdf. Accessed October 20, 2020.
9. Pharmacopeia E. *European Pharmacopeia 9.0*. Carbamazepine Monograph; 2017.
10. Pharmacopeia US. *USP 42 - NF 37. The United States Pharmacopeia*. 42 ed. Rockville, MD: The United States Pharmacopeial Convention, Inc; 2019.
11. Novartis. *Tegretol (carbamazepine USP)*. East Hanover, NJ: Food and Drug Administration U.S; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016608s101,018281s048lbl.pdf. Accessed November 26, 2018.
12. Bauer. *Applied Clinical Pharmacokinetics*. second ed. US: McGraw-Hill; 2008.
13. Maan JS, Saadabadi A. Carbamazepine. In: *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2018. https://www.ncbi.nlm.nih.gov/books/NBK482455/. Accessed November 15, 2018.
14. Bialer M, Levy RH, Perucca E. Does carbamazepine have a narrow therapeutic plasma concentration range? *Ther Drug Monit*. 1998;20(1):56-59.
15. Ghannoum M, Yates C, Galvao TF, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol*. 2014;52(10):993-1004.
16. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide. An update. *Clin Pharmacokinet*. 1986;11(3):177-198.
17. Tothfalusi L, Speidl S, Endrenyi L. Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. *Br J Clin Pharmacol*. 2008;65(1):110-122.
18. Callaghan N, O'Callaghan M, Duggan B, Feely M. Carbamazepine as a single drug in the treatment of epilepsy. A prospective study of serum levels and seizure control. *J Neurol Neurosurg Psychiatry*. 1978;41(10):907-912.
19. Lesser RP, Pippenger CE, Luders H, Dinner DS. High-dose monotherapy in treatment of intractable seizures. *Neurology*. 1984;34(6):707-711.
20. Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. *Lancet*. 1999;354(9172):13-19.
21. Schmidt S, Schmitz-Buhl M. Signs and symptoms of carbamazepine overdose. *J Neurol*. 1995;242(3):169-173.
22. Greenberg RG, Melloni C, Wu H, et al. Therapeutic index estimation of antiepileptic drugs: a systematic literature review approach. *Clin Neuropharmacol*. 2016;39(5):232-240.
23. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet*. 1995;345(8948):476-479.
24. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Res*. 1996;23(2):149-155.
25. Yacobi A, Zlotnick S, Colaizzi JL, et al. A multiple-dose safety and bioequivalence study of a narrow therapeutic index drug: a case for carbamazepine. *Clin Pharmacol Ther*. 1999;65(4):389-394.
26. Olling M, Mensinga TT, Barends DM, Groen C, Lake OA, Meulenbelt J. Bioavailability of carbamazepine from four different products and the occurrence of side effects. *Biopharm Drug Dispos*. 1999;20(1):19-28.
27. FDA. *Food and Drug Administration, U.S. Draft Guidance on Carbamazepine*. Food and Drug Administration; 2011. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM270381.pdf. Accessed February 5, 2019.
28. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med*. 1992;327(11):765-771.
29. FDA. Food and Drug Administration, U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). In: *Orange Book: Approved. DRUG Products with Therapeutic Equivalence Evaluations; 2018*. MD, USA: Food and Drug Administration; 2018. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 20, 2020.
30. Behme RJ, Brooke D. Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis. *J Pharm Sci*. 1991;80(10):986-990.
31. Grzesiak AL, Lang M, Kim K, Matzger AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *J Pharm Sci*. 2003;92(11):2260-2271.
32. Lang M, Kampf JW, Matzger AJ. Form IV of carbamazepine. *J Pharm Sci*. 2002;91(4):1186-1190.
33. Roberts RJ, Rowe RC. Influence of polymorphism on the Young's modulus and yield stress of carbamazepine, sulfathiazole and sulfanilamide. *Int J Pharm*. 1996;129:79-94.
34. Kobayashi Y, Ito S, Itai S, Yamamoto K. Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. *Int J Pharm*. 2000;193(2):137-146.
35. Tian F, Zeitler JA, Strachan CJ, Saville DJ, Gordon KC, Rades T. Characterizing the conversion kinetics of carbamazepine polymorphs to the dihydrate in aqueous suspension using Raman spectroscopy. *J Pharm Biomed Anal*. 2006;40(2):271-280.
36. Deng J, Staufenbiel S, Bodmeier R. Evaluation of a biphasic in vitro dissolution test for estimating the bioavailability of carbamazepine polymorphic forms. *Eur J Pharm Sci*. 2017;105:64-70.
37. Murphy D, Rodriguez-Cintron F, Langevin B, Kelly RC, Rodriguez-Hornedo N. Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder. *Int J Pharm*. 2002;246(1-2):121-134.
38. Flicker F, Eberle VA, Betz G. Variability in commercial carbamazepine samples–impact on drug release. *Int J Pharm*. 2011;410(1-2):99-106.
39. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res (N Y)*. 1995;12(3):413-420.
40. Beig A, Miller JM, Dahan A. Accounting for the solubility-permeability interplay in oral formulation development for poor water solubility drugs: the effect of PEG-400 on carbamazepine absorption. *Eur J Pharm Biopharm*. 2012;81(2):386-391.
41. Ikinci G, Capan Y, Senel S, Dalkara T, Hincal AA. Formulation and in vitro/in vivo investigation of carbamazepine controlled-release matrix tablets. *Pharmazie*. 1999;54(2):139-141.
42. Kasim NA, Whitehouse M, Ramachandran C, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol Pharm*. 2004;1(1):85-96.
43. Lake OA, Olling M, Barends DM. In vitro/in vivo correlations of dissolution data of carbamazepine immediate release tablets with pharmacokinetic data obtained in healthy volunteers. *Eur J Pharm Biopharm*. 1999;48(1):13-19.
44. Lee H, Park SA, Sah H. Surfactant effects upon dissolution patterns of carbamazepine immediate release tablet. *Arch Pharm Res (Seoul)*. 2005;28(1):120-126.
45. Mittapalli PK, Suresh B, Hussaini SS, Rao YM, Apte S. Comparative in vitro study of six carbamazepine products. *AAPS PharmSciTech*. 2008;9(2):357-365.
46. El-Massik MA, Abdallah OY, Galal S, Daabis NA. Towards a universal dissolution medium for carbamazepine. *Drug Dev Ind Pharm*. 2006;32(7):893-905.
47. Soderlind E, Karlsson E, Carlsson A, et al. Simulating fasted human intestinal fluids: understanding the roles of lecithin and bile acids. *Mol Pharm*. 2010;7(5):1498-1507.
48. Obata K, Sugano K, Saitoh R, et al. Prediction of oral drug absorption in humans by theoretical passive absorption model. *Int J Pharm*. 2005;293(1-2):183-192.
49. Scheytt T, Mersmann P, Lindstädt R, Heberer T. 1-octanol/water partition coefficients of 5 pharmaceuticals from human medical care: carbamazepine, clofibric acid, diclofenac, ibuprofen, and propyphenazone. *Water Air Soil Pollut*. 2005;165:3-11.
50. Kovacevic I, Parojcic J, Homsek I, Tubic-Grozdanis M, Langguth P. Justification of biowaiver for carbamazepine, a low soluble high permeable compound, in solid dosage forms based on IVIVC and gastrointestinal simulation. *Mol Pharm*. 2009;6(1):40-47.
51. Faigle JW, Feldman F. Pharmacokinetic data of carbamazepine and its major metabolites in man. In: Schneider H, Janz D, Gardner-Thorpe C, Meinardi H, Sherwin AL, eds. *Clinical Pharmacology of Anti-epileptic Drugs*. Berlin, Heidelberg: Springer; 1975.
52. Gerardin A, Dubois JP, Moppert J, Geller L. Absolute bioavailability of carbamazepine after oral administration of a 2% syrup. *Epilepsia*. 1990;31(3):334-338.
53. Schneider HJD, Gardner-Thorpe C, Meindardi H, Sherwin AL. *Clinical Pharmacology of Anti-epileptic Drugs*. New Yor, Heldelberg, Berlin: Springer-Verlag; 1975.
54. Lundbeck. *U.S. FDA Approves Carnexiv™ (Carbamazepine) Injection as Intravenous Replacement Therapy for Oral Carbamazepine Formulation*. Copenhagen, DK: H. Lundbeck A/S; 2016. https://investor.lundbeck.com/static-files/9ebea97f-f286-4a6c-a61f-6bed362c2e39. Accessed November 26, 2018.

55. Marino SE, Birnbaum AK, Leppik IE, et al. Steady-state carbamazepine pharmacokinetics following oral and stable-labeled intravenous administration in epilepsy patients: effects of race and sex. *Clin Pharmacol Ther*. 2012;91(3):483-488.
56. Tolbert D, Cloyd J, Biton V, et al. Bioequivalence of oral and intravenous carbamazepine formulations in adult patients with epilepsy. *Epilepsia*. 2015;56(6):915-923.
57. Anttila M, Kahela P, Panelius M, Yrjana T, Tikkanen R, Aaltonen R. Comparative bioavailability of two commercial preparations of carbamazepine tablets. *Eur J Clin Pharmacol*. 1979;15(6):421-425.
58. Rawlins MD, Collste P, Bertilsson L, Palmer L. Distribution and elimination kinetics of carbamazepine in man. *Eur J Clin Pharmacol*. 1975;8(2):91-96.
59. Bertilsson L. Clinical pharmacokinetics of carbamazepine. *Clin Pharmacokinet*. 1978;3(2):128-143.
60. Levy RH, Pitlick WH, Troupin AS, Green JR, Neal JM. Pharmacokinetics of carbamazepine in normal man. *Clin Pharmacol Ther*. 1975;17(6):657-668.
61. Meyer MC, Straughn AB, Jarvi EJ, Wood GC, Pelsor FR, Shah VP. The bioinequivalence of carbamazepine tablets with a history of clinical failures. *Pharm Res (N Y)*. 1992;9(12):1612-1616.
62. Veng-Pedersen P, Gobburu JV, Meyer MC, Straughn AB. Carbamazepine level-A in vivo-in vitro correlation (IVIVC): a scaled convolution based predictive approach. *Biopharm Drug Dispos*. 2000;21(1):1-6.
63. Zhang X, Lionberger RA, Davit BM, Yu LX. Utility of physiologically based absorption modeling in implementing quality by design in drug development. *AAPS J*. 2011;13(1):59-71.
64. Alsenz J, Haenel E. Development of a 7-day, 96-well Caco-2 permeability assay with high-throughput direct UV compound analysis. *Pharm Res (N Y)*. 2003;20(12):1961-1969.
65. Faassen F, Vogel G, Spanings H, Vromans H. Caco-2 permeability, P-glycoprotein transport ratios and brain penetration of heterocyclic drugs. *Int J Pharm*. 2003;263(1-2):113-122.
66. Fortuna A, Alves G, Falcao A, Soares-da-Silva P. Evaluation of the permeability and P-glycoprotein efflux of carbamazepine and several derivatives across mouse small intestine by the Ussing chamber technique. *Epilepsia*. 2012;53(3):529-538.
67. Kratz JM, Teixeira MR, Koester LS, Simoes CM. An HPLC-UV method for the measurement of permeability of marker drugs in the Caco-2 cell assay. *Braz J Med Biol Res*. 2011;44(6):531-537.
68. Krstic M, Popovic M, Dobricic V, Ibric S. Influence of solid drug delivery system formulation on poorly water-soluble drug dissolution and permeability. *Molecules*. 2015;20(8):14684-14698.
69. Owen A, Pirmohamed M, Tettey JN, Morgan P, Chadwick D, Park BK. Carbamazepine is not a substrate for P-glycoprotein. *Br J Clin Pharmacol*. 2001;51(4):345-349.
70. Patil SR, Kumar L, Kohli G, Bansal AK. Validated HPLC method for concurrent determination of antipyrine, carbamazepine, Furosemide and phenytoin and its application in assessment of drug permeability through caco-2 cell monolayers. *Sci Pharm*. 2012;80(1):89-100.
71. Winiwarter S, Bonham NM, Ax F, Hallberg A, Lennernas H, Karlen A. Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. *J Med Chem*. 1998;41(25):4939-4949.
72. Dickens D, Yusof SR, Abbott NJ, et al. A multi-system approach assessing the interaction of anticonvulsants with P-gp. *PLoS One*. 2013;8(5):e64854.
73. Luna-Tortos C, Fedrowitz M, Loscher W. Several major antiepileptic drugs are substrates for human P-glycoprotein. *Neuropharmacology*. 2008;55(8):1364-1375.
74. Cerveny L, Pavek P, Malakova J, Staud F, Fendrich Z. Lack of interactions between breast cancer resistance protein (bcrp/abcg2) and selected antiepileptic agents. *Epilepsia*. 2006;47(3):461-468.
75. Eichelbaum M, Ekbom K, Bertilsson L, Ringberger VA, Rane A. Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. *Eur J Clin Pharmacol*. 1975;8(5):337-341.
76. Garg SK, Kumar N, Bhargava VK, Prabhakar SK. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther*. 1998;64(3):286-288.
77. Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol*. 1994;47(11):1969-1979.
78. Mesdjian E, Seree E, Charvet B, et al. Metabolism of carbamazepine by CYP3A6: a model for in vitro drug interactions studies. *Life Sci*. 1999;64(10):827-835.
79. Bonin B, Vandel P, Vandel S, Kantelip JP. Effect of grapefruit intake on carbamazepine bioavailability: a case report. *Therapie*. 2001;56(1):69-71.
80. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet*. 2000;38(1):41-57.
81. Mochizuki K, Hamano Y, Miyama H, Arakawa K, Kobayashi T, Imamura H. Successful treatment of a case with concurrent ingestion of carbamazepine overdose and grapefruit juice. *Acute Med Surg*. 2016;3(1):36-38.
82. Gonzalez-Garcia I, Mangas-Sanjuan V, Merino-Sanjuan M, et al. IVIVC approach based on carbamazepine bioequivalence studies combination. *Pharmazie*. 2017;72(8):449-455.
83. Popovic J, Mikov M, Jakovljevic V. Pharmacokinetics of carbamazepine derived from a new tablet formulation. *Eur J Drug Metab Pharmacokinet*. 1995;20(4):297-300.
84. Kayali A, Tuglular I, Ertas M. Pharmacokinetics of carbamazepine. Part I: a new bioequivalency parameter based on a relative bioavailability trial. *Eur J Drug Metab Pharmacokinet*. 1994;19(4):319-325.
85. Revankar SN, Desai ND, Bhatt AD, et al. Comparison of absorption rate and bioavailability of two brands of carbamazepine. *J Assoc Phys India*. 1999;47(7):699-702.
86. Silpakit O, Amornpichetkoon M, Kaojarern S. Comparative study of bioavailability and clinical efficacy of carbamazepine in epileptic patients. *Ann Pharmacother*. 1997;31(5):548-552.
87. Savolainen M, Kogermann K, Heinz A, et al. Better understanding of dissolution behaviour of amorphous drugs by in situ solid-state analysis using Raman spectroscopy. *Eur J Pharm Biopharm*. 2009;71(1):71-79.
88. Zhou Y, Chu W, Lei M, Li J, Du W, Zhao C. Application of a continuous intrinsic dissolution-permeation system for relative bioavailability estimation of polymorphic drugs. *Int J Pharm*. 2014;473(1-2):250-258.
89. Kahela P, Aaltonen R, Lewing E, Anttila M, Kristoffersson E. Pharmacokinetics and dissolution of two crystalline forms of carbamazepine. *Int J Pharm*. 1983;14(1):103-112.
90. Elqidra R, Ünlü N, Çapan Y, Sahin G, Dalkara T, Hincal AA. Effect of polymorphism on in vitro-in vivo properties of carbamazepine conventional tablets. *J Drug Deliv Sci Technol*. 2004;14(2):147-153.
91. Chan KK, Sawchuk RJ, Thompson TA, et al. Bioequivalence of carbamazepine chewable and conventional tablets: single-dose and steady-state studies. *J Pharm Sci*. 1985;74(8):866-870.
92. Cornaggia C, Gianetti S, Battino D, et al. Comparative pharmacokinetic study of chewable and conventional carbamazepine in children. *Epilepsia*. 1993;34(1):158-160.
93. Dam M, Christiansen J, Kristensen CB, Helles A, Jaegerskou A, Schmiegelow M. Carbamazepine: a clinical biopharmaceutical study. *Eur J Clin Pharmacol*. 1981;20(1):59-64.
94. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm Res (N Y)*. 1989;6(7):612-618.
95. Medina JR, Salazar DK, Hurtado M, Cortes AR, Dominguez-Ramirez AM. Comparative in vitro dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system. *Saudi Pharm J*. 2014;22(2):141-147.
96. Kaneniwa N, Umezawa O, Watari N, Kawakami K, Asami H, Sumi M. [Bioavailability and dissolution test of commercial carbamazepine tablets]. *Yakugaku Zasshi*. 1984;104(1):83-90.
97. Jung H, Milán RC, Girard ME, León F, Montoya MA. Bioequivalence study of carbamazepine tablets: in vitro/in vivo correlation. *Int J Pharm*. 1997;152(1):37-44.
98. Bonlokke L, Hovgaard L, Kristensen HG, Knutson L, Lindahl A, Lennernas H. A comparison between direct determination of in vivo dissolution and the deconvolution technique in humans. *Eur J Pharm Sci*. 1999;8(1):19-27.
99. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. *Eur J Pharm Biopharm*. 2000;50(1):3-12.
100. Sethia S, Squillante E. In vitro-in vivo evaluation of supercritical processed solid dispersions: permeability and viability assessment in Caco-2 cells. *J Pharm Sci*. 2004;93(12):2985-2993.
101. Kubbinga M, Langguth P, Barends D. Risk analysis in bioequivalence and biowaiver decisions. *Biopharm Drug Dispos*. 2013;34(5):254-261.
102. Meyer MC, Straughn AB, Mhatre RM, Shah VP, Williams RL, Lesko LJ. The relative bioavailability and in vivo-in vitro correlations for four marketed carbamazepine tablets. *Pharm Res (N Y)*. 1998;15(11):1787-1791.
103. Bermejo M, Meulman J, Davanco MG, Carvalho PO, Gonzalez-Alvarez I, Campos DR. In vivo predictive dissolution (IPD) for carbamazepine formulations: additional evidence regarding a biopredictive dissolution medium. *Pharmaceutics*. 2020;12(6).
104. Oles KS, Penry JK, Smith LD, Anderson RL, Dean JC, Riela AR. Therapeutic bioequivalency study of brand name versus generic carbamazepine. *Neurology*. 1992;42(6):1147-1153.
105. Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. *J Pharm Pharmacol*. 1991;43(2):117-119.
106. Homsek I, Parojcic J, Cvetkovic N, Popadic D, Djuric Z. Biopharmaceutical characterization of carbamazepine immediate release tablets. In vitro-in vivo comparison. *Arzneim Forsch*. 2007;57(8):511-516.