Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Codeine Phosphate

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ABSTRACT: The present monograph reviews data relevant to applying the biowaiver procedure for the approval of immediate-release multisource solid dosage forms containing codeine phosphate. Both biopharmaceutical and clinical data of codeine were assessed. Solubility studies revealed that codeine meets the “highly soluble” criteria according to World Health Organization (WHO), the European Medicines Agency (EMA), and the United States Food and Drug Administration (US FDA). Codeine's fraction of dose absorbed in humans was reported to be high (>90%) based on cumulative urinary excretion of drug and drug-related material following oral administration. The permeability of codeine was also assessed to be high in both Caco-2 monolayers and rat intestinal perfusion studies. The main risks associated with codeine, that is, toxicity (attributed to CYP2D6 polymorphism) and its abuse potential, are present irrespective of the dosage form, and do not need to be taken into account for bioequivalence (BE) considerations. Taken together, codeine is a class 1 drug with manageable risk and is a good candidate for waiver of in vivo BE studies. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1592–1600, 2014

Keywords: absorption; bioavailability; bioequivalence; biopharmaceutics classification system (BCS); codeine phosphate; permeability; dissolution; solubility

INTRODUCTION

The present biowaiver monograph addresses the active pharmaceutical ingredient (API) codeine phosphate. This monograph is a part of the biowaiver monograph series by the International Pharmaceutical Federation (FIP) that currently contains over 40 monographs (http://www.fip.org/bcs). The purpose of this series is to assess whether in vivo pharmacokinetic bioequivalence (BE) studies can be safely waived in favor of in vitro dissolution studies for the approval of new immediate-release (IR) solid oral dosage forms of a given API. Each monograph is based on a comprehensive literature review, which forms the basis of the risk–benefit analysis of applying a biowaiver-based approval to new or extensively revised formulations of the given API. Some of the properties discussed include the solubility of the API, pharmacokinetics and permeability data, the therapeutic use and therapeutic index, data on excipient interactions, and any problems that have been reported with bioavailability (BA) and/or BE. On the basis of these properties, a risk–benefit analysis is performed and a decision to recommend or advise against biowaivers for the given API is made.

GENERAL CHARACTERISTICS

Scope

This monograph refers exclusively to the phosphate salt of codeine. The analysis is relevant primarily for oral formulations in which codeine phosphate is the sole active ingredient; it may also be applied for combination products containing codeine phosphate. However, for combination products, the other APIs and their potential interaction with codeine phosphate should be analyzed as well. Modified/extended release formulations are also out of the scope of this analysis.

Name

Codeine is an opioid derived from the unripe seed capsules of the poppy plant (Papaver somniferum), and it has a similar structure to morphine, with a methyl substitution on the
As a result, the expected CYP2D6 phenotype. The keywords used for searching were: codeine, intestinal absorption, BA, BE, log P, solubility, permeability, pharmacokinetics, polymorphism, 2D6, mass balance, metabolism, and radiolabeled studies.

**Solubility Experiments**

For the solubility experiments, a standard shake-flask method was applied using three different aqueous media with pH values of 1.0 (maleate buffer), 4.5 (acetate buffer), and 7.5 (phosphate buffer) at 37 °C. Solubility studies were performed at the Department of Clinical Pharmacology, Ben-Gurion University of the Negev, Beer-Sheva, Israel, using analytical grade codeine phosphate (generously donated by Rekah Pharmaceutical Industry Ltd., Holon, Israel). The establishment of equilibrium was confirmed by comparison of 24- and 48-h samples. The pH was measured both before and after the experiment, to assure that the solubility was indeed registered at the correct pH. Drug levels in the samples were analyzed by ultraperformance liquid chromatography (UPLC), using a previously described method.\textsuperscript{17} Three replicates were carried out in each pH condition.

**Permeability Experiments**

The effective permeability coefficient (P\textsubscript{eff}) of codeine versus metoprolol was determined in situ using the single-pass rat intestinal perfusion model. The experimental procedure followed previous reports.\textsuperscript{18–20}

To account for the complexity of the whole of the small intestine, permeability was determined in three different 10-cm segments: a proximal jejunal segment, mid-small intestinal segment, and a distal ileal segment.\textsuperscript{21–23} Briefly, each intestinal segment was cannulated on two ends, and was perfused with the corresponding phosphate buffer containing codeine and metoprolol. The concentrations of codeine and metoprolol in the perfusion buffers were 240 and 400 µg/mL, respectively, to represent the maximal dose of the drugs (60 and 100 mg, respectively) in 250 mL. The physiological pH of the perfused small intestinal region dictated the pH throughout the experiment: (1) proximal jejunum, pH 6.5; (2) middle small intestine,
pH 7.0; and (3) distal ileum, pH 7.5.\textsuperscript{24} Steady-state conditions were ensured by conducting an initial 60-min perfusion, followed by additional 60 min with samples taken every 10 min and immediate UPLC analysis.\textsuperscript{17} At the end of the experiment, the length of each perfused intestinal segment was accurately measured.\textsuperscript{25,26} Additionally, the pH of the collected samples was measured to verify that there was no pH change during the perfusion.

The $P_{\text{eff}}$ (cm/s) through the rat gut wall was determined according to the following equation:

$$P_{\text{eff}} = \frac{-Q\ln(C_{\text{out}}/C_{\text{in}})}{2\pi RL}$$

where $Q$ is the perfusion buffer flow rate (0.2 mL/min), $C_{\text{out}}/C_{\text{in}}$ is the ratio of the outlet and the inlet concentration of drug that has been adjusted for water transport\textsuperscript{27–29} $R$ is the radius of the intestinal segment (set to 0.2 cm), and $L$ is the length of the perfused intestinal segment.

**CHEMICAL PROPERTIES**

**Polymorphism**

No information on whether codeine exhibits polymorphism in the solid state could be identified in the literature. One should not confuse this term with the genetic polymorphism of the metabolic enzyme CYP2D6, which is involved with the metabolism of codeine and is discussed hereinafter.

**Dosage Form Strengths and Dose**

Oral dosage forms that contain codeine phosphate as the only active ingredient exist in several countries, with dosage strengths that ranges between 15 and 60 mg.

The WHO (http://www.who.int), and Canadian guideline for safe and effective use of opioids for chronic noncancer pain\textsuperscript{9} register a maximal dose of 30 mg for codeine phosphate, although the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines specify a maximal dose of up to 60 mg every 4 h.\textsuperscript{11}

**Solubility**

The Merck Index and Martindale report codeine phosphate as being “freely soluble in water.” Because the solubility data for codeine phosphate available in the literature do not cover the pH range of 1.0–7.5 at 37°C, as required by the FDA guidelines,\textsuperscript{30} additional solubility investigations were performed to classify its solubility properties according to the Biopharmaceutics Classification System (BCS).

According to the FDA, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1–7.5. This can be demonstrated through the calculation of the dose number ($D_0$) according to the equation:

$$D_0 = M/V_0/C_S$$

where $M$ is the highest dose strength, $V_0$ is set at 250 mL, and $C_S$ is the equilibrium solubility of the drug. A $D_0$ value of $\leq 1$ means that the highest dose strength is soluble in 250 mL of the investigated aqueous media, and hence indicates “high solubility.” For codeine phosphate, with highest dose strength of 60 mg, the minimal solubility that would lead to the “high solubility” classification is 0.24 mg/mL. We found that the solubility of codeine exceeded 120 mg/mL throughout the pH range of 1–7.5, which means that the $D_0$ of codeine is lower than 0.002, unequivocally indicating a BCS high-solubility classification.

**Partition Coefficient**

Codeine is a moderately lipophilic compound and has a log $P$ value of 1.1 (octanol–water).\textsuperscript{31} At the small intestinal pH, 6.5–7.5, codeine has positive log $D$ values, ranging from 0.25 (log $D_{6.5}$) to 0.6 (log $D_{7.5}$) (Table 1).

**pKa**

Codeine is a weak base and has a pKa value of 8.2.\textsuperscript{32}

**PHARMACOKINETIC PROPERTIES**

**Absorption and BA**

Codeine has a relatively low BA (50%),\textsuperscript{1} which is likely because of the extensive first-pass effect rather than poor absorption. Indeed, codeine’s human fraction of dose absorbed ($F_{\text{abs}}$) was reported to be high (>90%) based on cumulative urinary excretion of drug and drug-related material (chiefly codeine-6-glucuronide), following oral administration.\textsuperscript{33–36} Although no studies with radiolabeled codeine could be found in the literature to support $F_{\text{abs}}$, the high-cumulative urinary excretion of drug and drug-related material is a very strong evidence for $F_{\text{abs}}$. Passive permeation is probably the main mechanism responsible for the absorption of codeine, as no information on transporter-mediated absorption of codeine could be found in the literature. Moreover, similar apical to basolateral (a→b) and basolateral to apical (b→a) permeability of codeine across Caco-2 cell monolayers was reported.\textsuperscript{35} As the involvement of transporters, either efflux or uptake, may result in an asymmetrical permeability, the similar a→b and b→a permeability suggests passive absorption,\textsuperscript{37,38} although it is recognized, theoretically at least, that trade-offs, for example, between simultaneous efflux and influx transporters, could balance each other. Similar absorption of oral and rectal dosage forms of codeine\textsuperscript{39} also suggests passive permeability as the main absorptive mechanism, because the expression of transporters is very unlikely to be similar in the small intestine and in the colon.\textsuperscript{40} Neither dose linearity nor food effect studies for codeine phosphate are available in the literature.

**Permeability**

The permeability of codeine across Caco-2 cell monolayers was assessed by Skolnik et al.\textsuperscript{35} The apparent permeability ($P_{\text{app}}$) of codeine was $2.29 \times 10^{-5}$ cm/s in the a→b direction and $1.99 \times 10^{-5}$ cm/s in the b→a direction. In comparison, the $P_{\text{app}}$
of metoprolol, the benchmark for low/high permeability class boundary, was $1.77 \times 10^{-5}$ cm/s in the a→b direction and $9.28 \times 10^{-6}$ cm/s in the b→a direction. For further comparison, values for the low-permeability drug cimetidine were $6.64 \times 10^{-6}$ cm/s in the absorptive and secretory directions. Thus, the permeability of codeine exceeds that of metoprolol, in the same laboratory, and codeine is therefore classified as a high-permeability drug according to this study. Furthermore, the similar permeability of codeine in both the absorptive and secretory directions indicates that the main mechanism of codeine absorption is passive permeation, with little or no involvement of transporters.

To further validate this result, we conducted in situ permeability studies of codeine phosphate versus metoprolol using the single-pass rat intestinal perfusion method.

The experimental procedure followed previous reports. Similar permeability was revealed for codeine and metoprolol throughout the entire small intestine; codeine and metoprolol permeability values were $3.5 \times 10^{-5}$ and $3.6 \times 10^{-5}$ cm/s in the proximal jejunum, $7.8 \times 10^{-5}$ and $7.2 \times 10^{-5}$ cm/s in the middle small intestine, and $1.3 \times 10^{-4}$ and $1.2 \times 10^{-4}$ cm/s in the distal ileum, respectively (Table 2). These results corroborate the findings of Skolnik et al. and provide further evidence that codeine is a high-permeability drug.

**Distribution, Metabolism, and Elimination**

Codeine has a volume of distribution ($V_d$) of $3–7$ L/kg and is widely distributed throughout the body. Codeine is extensively metabolized by the liver, predominantly to codeine-6-glucuronide, and in small part to norcodeine by CYP3A4. A small fraction of codeine is converted by CYP2D6 to morphine, which is responsible for both the pharmacological activity and toxic effects of codeine. Only about 3%–5% of codeine dose is excreted unchanged in the urine. The elimination half-life of codeine was reported to be 1.8 h. Quite variable clearance was reported in the literature, ranging from 40 to 140 L/h.

**DOSAGE FORM PERFORMANCE**

**Excipients**

The excipients of several marketed IR solid oral drug products containing codeine phosphate as single API are given in Table 3. No specific studies about possible effects of these excipients on codeine release and absorption have been reported to date. Moreover, the products are marketed in ICH associated countries, and hence, one may assume that they have passed a rigorous BE study, indicating that the excipients, in the amounts used, do not interfere with codeine absorption.

**In Vivo BE**

No BE studies of drug products containing codeine as a single API were found in the literature. However, several IR combination drug products containing codeine phosphate have been demonstrated to be bioequivalent and the results are summarized in Table 4.

In an open, two treatment, two period crossover study in 24 subjects, a test product containing aspirin, butalbital, caffeine, and codeine (325/50/40/30 mg) produced by Jerome Stevens was found to be bioequivalent to a reference product (Sandoz’s Fiorinal); The dose used in the study consisted of two capsules from each product, bringing the total administered dose of codeine to 60 mg. The 90% confidence interval (CI) values of the test to reference (T/R) ratios for AUC$_{0-\infty}$, AUC$_{0-\infty}$, and $C_{max}$ for codeine were 0.92–1.08, 0.93–1.06, and 0.99–1.14, respectively (www.accessdata.fda.gov/drugsatfda_docs/nda/99/74-951_Butalbital,%20Aspirin,%20Caffeine,%20and%20Codeine%20Phosphate_Bioeqr.pdf).

An additional two-way crossover BE study between a similar combination drug product (aspirin, butalbital, caffeine, and codeine; 325/50/40/30 mg) manufactured by Endo pharmaceuticals and the same reference formulation (Sandoz’s Fiorinal) was performed in 24 subjects. Again, the total administered dose of codeine was 60 mg. The 90% CI values of the test to reference (T/R) ratios for AUC$_{0-\infty}$, AUC$_{0-\infty}$, and $C_{max}$ for codeine were 0.98–1.10, 0.99–1.11, and 0.95–1.14, respectively (www.accessdata.fda.gov/drugsatfda_docs/nda/99/75-351_Butalbital_bioeqr.pdf).

A randomized, single dose, open-labeled two-period crossover study compared a test formulation of ibuprofen and codeine (200/12.8 mg) produced by The Boots Company PLC (UK) to the reference formulation Nurofen Plus (Crookes Healthcare Limited, UK). The 90% CI values of the test to reference (T/R) ratios for AUC$_{0-\infty}$, AUC$_{0-\infty}$, and $C_{max}$ for codeine were 0.91–1.00, 0.91–1.00, and 0.86–0.97, respectively (www.mhra.gov.uk/home/groups/par/documents/websitesresources/con103096.pdf).

It should be noted that the dissolution of the products described above follows the USP requirements, but does not meet the FDA biowaiver dissolution criterion.

**Dissolution**

In the first two aforementioned BE studies, a dissolution assay was performed under the conditions specified by the USP for capsules containing the combination aspirin, butalbital, caffeine, and codeine. The tests were run using USP apparatus 2 in 50 rpm for 60 min, with a medium of 1000 mL of water. In both studies, both the reference and the test products met the USP dissolution requirements of minimum 75% of the amount of active ingredients dissolved within 60 min. The third BE study did not specify whether dissolution studies were conducted.

**DISCUSSION**

**Solubility**

Taking 60 mg as the highest dose strength of codeine, the minimal solubility that would allow the “high solubility” classification is 0.24 mg/mL. We found that the solubility of codeine

| Table 2. Effective Permeability Values ($P_{eff}$, $\times 10^{-5}$ cm/s) Obtained for Codeine and Metoprolol After In Situ Single-Pass Perfusion to the Rat Proximal Jejunum at pH 6.5, Middle Small Intestine at pH 7.0, and to the Distal Ileum at pH 7.5 |
|---|---|---|
| | Proximal Jejunum; pH 6.5 | Middle Small Intestine; pH 7.0 | Distal Ileum; pH 7.5 |
| Codeine | 3.5 (0.7) | 7.8 (1.9) | 13.1 (1.1) |
| Metoprolol | 3.6 (1.1) | 7.2 (0.9) | 12.6 (2.8) |

Mean (SD); $n = 6$ in each experimental group.
Table 3. Excipients * Present in Codeine Phosphate IR Solid Oral Drug Products with a Marketing Authorization (MA) in Canada (CA), Czech Republic (CZ), Germany (DE), Denmark (DK), Spain (ES), France (FR), Ireland (IE), The Netherlands (NL), Norway (NO), Romania (RO), Sweden (SE), Slovakia (SK), and United Kingdom (UK), and the Minimal and Maximal Amount of that Excipient Present per Dosage Unit in Solid Oral Drug Products with a MA in the US.  

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Drug Products Containing That Excipient with a MA Granted by the Named Country</th>
<th>Range Present in Solid Oral Dosage Forms with a MA in the US (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acacia</td>
<td>UK(1)</td>
<td>5–156</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate</td>
<td>ES(2)</td>
<td>104–850</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>CA(3,4), DK(5,6), ES(2), FR(7), IS(8), NL(9), NO(10), RO(11), and SE(12)</td>
<td>4.6–1385</td>
</tr>
<tr>
<td>Cellulose, powdered</td>
<td>DE(13)</td>
<td>44–170</td>
</tr>
<tr>
<td>Crosscarmellose sodium</td>
<td>CA(3)</td>
<td>2–180</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>DE(14)</td>
<td>4.4–792</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>DE(15)</td>
<td>1.0–121</td>
</tr>
<tr>
<td>Gelatin</td>
<td>CZ(16), DE(15), DK(5,6,17), IS(8), NO(10), RO(18,19), SE(12), and SK(20)</td>
<td>1–756</td>
</tr>
<tr>
<td>Hypromellose</td>
<td>DK(6) and NO(10)</td>
<td>0.8–537</td>
</tr>
<tr>
<td>Lactose</td>
<td>CA(3,4), CZ(16), DE(13,14,21,22), DK(5,6,17), IE(23), IS(8), NL(9,24), NO(10), RO(11,18,19,25–27), SE(12), SK(20), and UK(1,28)</td>
<td>23–1020</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>CA(3,4), CZ(16), DE(13–15,21), DK(5,6,17), ES(2), FR(7), IE(23), IS(8), NL(9,24), NO(10), RO(11,18,19,25–27), SE(12), SK(20), and UK(1,28)</td>
<td>0.15–401</td>
</tr>
<tr>
<td>Povidone</td>
<td>DE(14,15) and RO(25,26)</td>
<td>0.17–240</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>DK(6) and NO(10)</td>
<td>1.5–148</td>
</tr>
<tr>
<td>Silica</td>
<td>CA(3,4), DE(13,22), ES(2), IE(23), NL(9), and RO(11,26)</td>
<td>0.50–100</td>
</tr>
<tr>
<td>Sodium laurilsulfate</td>
<td>DE(15)</td>
<td>0.65–52</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>DE(13) and ES(2)</td>
<td>2–876</td>
</tr>
<tr>
<td>Sodium metabisulphite</td>
<td>IS(8) and SE(12)</td>
<td>0.36–8</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>DE(13)</td>
<td>5–337</td>
</tr>
<tr>
<td>Starch</td>
<td>CZ(16), DE(21,22), DK(5,6,17), IS(8), NL(9,24), NO(10), RO(11,18,19,25–27), SE(12), SK(20), and UK(1,28)</td>
<td>0.44–1135</td>
</tr>
<tr>
<td>Starch, pregelatinised</td>
<td>UK(28)</td>
<td>4.2–600</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>CA(4), DE(22), and UK(1,28)</td>
<td>0.9–72</td>
</tr>
<tr>
<td>Sucrose</td>
<td>DE(15)</td>
<td>12–900</td>
</tr>
<tr>
<td>Talc</td>
<td>CZ(16), DE(15,21), DK(5,6,17), ES(2), IS(8), NL(9), NO(10), RO(11,18,19,25–27), SE(12), SK(20)</td>
<td>0.1–220</td>
</tr>
</tbody>
</table>

*a: Colourants, water, and ingredients present in the coating are not included. Substances are excluded if it can be assumed that the constituents are only present in the coating/polish.


The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

Excluded are: combination products.

Excluded are: ingredients present in the coating are not included. Substances are excluded if it can be assumed that the constituents are only present in the coating/polish.
<table>
<thead>
<tr>
<th>Strength on Which BE Performed</th>
<th>Test Formulation</th>
<th>Manufacturer or License Holder</th>
<th>Composition</th>
<th>Reference Product</th>
<th>Study Design</th>
<th>Prandial</th>
<th>Bioequivalence Criteria/Statistics</th>
<th>Results</th>
<th>In Vitro Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg</td>
<td>Aspirin, butalbital, caffeine, and codeine (325/50/40/30 mg) produced by Jerome Stevens</td>
<td>Aspirin 325 mg Butalbital 50 mg Caffeine 40 mg Codeine phosphate 30 mg Excipients: starch, microcrystalline cellulose, talc, colloidal silicon dioxide, and stearic acid</td>
<td>Fiorinal (Sandoz Ltd.)</td>
<td>Open, two treatments, two periods crossover study</td>
<td>Fasting</td>
<td>90% CI ($C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$)</td>
<td>Bioequivalent Dissolution in water exceeded 75% within 60 min for both products, as required by the USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td>Aspirin, butalbital, caffeine, and codeine (325/50/40/30 mg) produced by Endo Pharmaceuticals</td>
<td>Aspirin 325 mg Butalbital 50 mg Caffeine 40 mg Codeine phosphate 30 mg Excipients: pregelatinized starch, microcrystalline cellulose, talc, sodium lauryl sulfate, colloidal silicon dioxide, and stearic acid</td>
<td>Fiorinal (Sandoz Ltd.)</td>
<td>Open, two treatments, two periods crossover study</td>
<td>Fasting</td>
<td>90% CI ($C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$)</td>
<td>Bioequivalent Dissolution in water exceeded 75% within 60 min for both products, as required by the USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.8 mg</td>
<td>Ibuprofen and codeine (200/12.8 mg) produced by The Boots Company PLC, UK</td>
<td>Ibuprofen 200 mg Codeine phosphate 12.8 mg Excipients: microcrystalline cellulose, hypromellose, sodium starch glycolate, pregelatinised maize starch, titanium dioxide, and talc</td>
<td>Nurofen Plus (Crookes Healthcare Limited, UK)</td>
<td>A randomized, single dose, open-labeled two-period crossover study</td>
<td>Fasting</td>
<td>90% CI ($C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$)</td>
<td>Bioequivalent N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
exceeded 120 mg/mL throughout the pH range of 1–7.5, which means that the $D_0$ of codeine is lower than 0.002, unequivocally indicating a BCS high-solubility classification.

**Permeability and Absorption**

Codeine has a human intestinal absorption of more than 90% based on cumulative urinary excretion of drug and drug-related material (chiefly codeine-6-glucuronide) following oral administration.  

Codeine was previously classified as high-permeability drug in Caco-2 monolayers study. This result was further strengthened by our rat perfusion study in three different segments throughout the small intestine, which showed that the permeability of codeine is similar to the reference drug metoprolol throughout the entire small intestine. Taken together, these results indicate that codeine may be safely classified as a high-permeability drug.

**BCS and BDDCS Classification**

Previously, Skolnik et al.  classified codeine as a BCS class 1 drug based on its high permeability across Caco-2 monolayers. Additional publications also classified codeine as a BCS class 1 compound. On the contrary, Kasim et al. and Takagi et al. used partition coefficient values for the classification of drug permeability, and because codeine's log $P$ (1.1) value is lower than that of the reference drug metoprolol (2.3), they provisionally classified codeine phosphate as a BCS class 3 drug. In general, a reasonable correlation exists between log $P$ values and jejunal permeability; however, a significant number of false-negative cases have been recorded, in which drugs with lower log $P$ than metoprolol exhibit complete absorption. These include antipyrine, cephalexin, D-glucose, levodopa, L-leucine, phenylalanine, piroxicam, valacyclovir, pseudoephedrine, and sotalol, indicating the difficulty of assigning BCS classification based merely on limited physicochemical characteristics.

On the basis of the urinary recovery data in humans, the work of Skolnik et al., and the experimental data presented in this monograph, it can be concluded that codeine phosphate can be safely classified as a BCS class 1 drug. Benet et al. classified codeine as a class 1 compound according to the Biopharmaceutics Drug Disposition Classification System (BDDCS) because of its high fraction of dose metabolized.

**Risks of Bioinequivalence Caused by Excipients and/or Manufacturing Parameters**

No information was found in the literature concerning potential influence of excipients or manufacturing process on the performance of codeine formulations.

**Patient’s Risks Associated with Bioinequivalence**

The main risk associated with bioequivalence of generic codeine formulations is codeine toxicity (i.e., CNS and respiratory depression) that is related to the conversion of codeine to morphine and is highly dependent on the CYP2D6 phenotype. The fraction of codeine dose converted to morphine is 5%–10% in EM; however, the amount of codeine converted to morphine may be higher in UM by as much as 80-fold compared with EM. For this reason, the CPIC Guidelines advise against the use of codeine in patients that were found to be UM by genetic screening. This complication, however, is present irrespective of the dosage form, and hence is unrelated to BE considerations.

It should also be noted that codeine has long been recognized as a drug of abuse, and despite this, it is incorporated in many OTC drug products. Again, the potential for abuse is irrespective of the dosage form, and hence should not be regarded as to BE considerations.

**CONCLUSIONS**

Codeine phosphate is a high-solubility, high-permeability drug, and is therefore classified as a BCS class 1 compound. The risk of bioequivalence is manageable as long as the use of codeine is avoided in UM. For these reasons, we consider codeine phosphate to be a good candidate for waiver of in vivo studies.

Granting a biowaiver for IR solid oral dosage forms containing codeine phosphate is scientifically justified, subjected to the following conditions: (1) the test product contains only excipients that are well known and used in normal amounts, for example, those tabulated for products with MA in ICH-associated countries (Table 3); and (2) both the test and comparator dosage forms enable very rapid dissolution of codeine, or, rapid dissolution with similarity of the dissolution profiles demonstrated at least at pH 1.2, 4.5, and 6.8 for codeine. For products containing other API(s) in addition to codeine, the possibility of a biowaiver for each API should be separately considered.

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**REFERENCES**


