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

ARIK DAHAN,[1] OMRI WOLK,[1] MORAN ZUR,[1] GORDON L. AMIDON,[2] BERTIL ABRAHAMSSON,[3] RODRIGO CRISTOFOLETTI,[4] D. W. GROOT,[5] SABINE KOPP,[6] PETER LANGGUTH,[7] JAMES E. POLLI,[8] VINOD P. SHAH,[9] JENNIFER B. DRESSMAN[10]

[1]Department of Clinical Pharmacology, School of Pharmacy, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel
[2]Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, Michigan
[3]Pharmaceutical Development, AstraZeneca R&D, Mölndal, Sweden
[4]Brazilian Health Surveillance Agency (Anvisa), Division of Bioequivalence, Brasilia, Brazil
[5]RIVM (National Institute for Public Health and the Environment), Bilthoven, The Netherlands
[6]World Health Organization, Geneva, Switzerland
[7]Institute of Pharmacy, Biopharmaceutics and Pharmaceutical Technology, Johannes Gutenberg-University, Mainz, Germany
[8]Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, Maryland
[9]International Pharmaceutical Federation (FIP), The Hague, The Netherlands
[10]Institute of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

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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

Correspondence to: Jennifer B. Dressman (Telephone: +49-69-7982-9680; Fax: +49-69-7982-9724; E-mail: dressman@em.uni-frankfurt.de)

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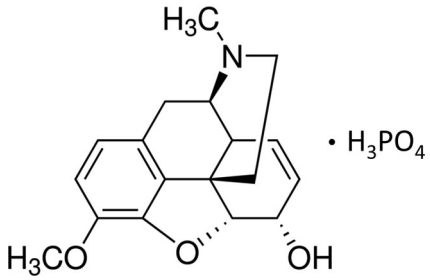

Figure 1. Molecular structure of codeine.

phenolic hydroxyl group.[1] The chemical description of the phosphate salt form is 7,8-didehydro-4,5 alpha-epoxy-3-methoxy-17-methylmorphinan-6 alpha-ol phosphate (1:1) and has the molecular formula of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$. Codeine has one chiral center. Its molecular weight is 406.4 g/mol and its melting point is 155°C (Merck Index). The structure of codeine phosphate is given in Figure 1.

Therapeutic Indication and Dose

Codeine phosphate demonstrated antitussive activity in several clinical trials performed between 1966 and 1984.[2] Although this effect was observed in patients suffering from chronic cough as a result of diseases such as bronchitis or chronic obstructive pulmonary disease, the prescription of codeine for acute cough has become a common practice over the years. However, more recent studies failed to demonstrate any antitussive effect of this drug when compared with placebo.[3,4] Therefore, codeine phosphate is currently recommended by the American College of Chest Physician (ACCP) for the alleviation of chronic but not acute cough.[5] Reports in the literature on the daily dose of codeine required for cough suppression ranges between 7.5 and 60 mg.[5]

Codeine is also indicated for the relief of mild to moderately severe pain. The analgesic properties of codeine stem from its conversion to morphine and morphine-6-glucuronide because codeine's affinity for μ-opioid receptors is 200-fold weaker than that of morphine.[6,7] Codeine has one chiral center, and some data suggest stereospecific analgesic (but not antitussive) effect of the *d*- and *l*-isomers.[8] Yet, to the best of our knowledge, all marketed products include the racemic mixture of codeine. The recommended initial dose for pain relief is 15–30 mg every 6 h. This dose can be increased in increments of 15–30 mg per day up to a total daily dose of 600 mg.[9]

Therapeutic Index and Toxicity

The main toxic effects of codeine are central nervous system (CNS) and respiratory depression, both of which stem from the conversion of codeine to morphine by CYP2D6.[10,11]

Codeine is not listed on the official list of narrow therapeutic index (NTI) drugs published by the National Institute of Health Sciences in Japan (http://www.nihs.go.jp) or in the NTI drug list of the US FDA published in 1988 (http://ecapps.health.state.pa.us). However, it is difficult to determine the therapeutic index of codeine, as both the effective and lethal dose are highly dependent on the genetic polymorphism of CYP2D6: the alleles *CYP2D6* may be characterized as having normal function, reduced function, or nonfunctional based on the expected activity level of the enzyme for which they encode. Each functional group is assigned an activity value ranging from 0 to 1.0 (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1.0 for fully functional). These values are used to assign a total activity score for each genotype; the majority of patients have an activity score of 1.0–2.0 and present an extended metabolizers (EM) phenotype. Roughly 2% of patients have an activity score greater than 2.0 and are ultrarapid metabolizer (UM), whereas patients with activity scores of 0.5 and 0 are intermediate metabolizers and poor metabolizers, respectively.[11,12] This polymorphism has significant influence on the efficacy and toxicity.[13] Indeed, cases of toxicity on the one hand and lack of therapeutic effect on the other hand have been documented, even when the standard dose was administered.[10,14,14–16] As a result, the expected CYP2D6 phenotype of the individual patient, as well as the specific population, must be taken into account whenever codeine administration is considered.[11]

METHODS

Literature Analysis

Literature data were obtained from PubMed, Micromedex, the Merck Index, and Goodman and Gilman's "The pharmacological basis of therapeutics" (11th edition). 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.[17] Three replicates were carried out in each pH condition.

Permeability Experiments

The effective permeability coefficient (P_{eff}) of codeine versus metoprolol was determined *in situ* using the single-pass rat intestinal perfusion model. The experimental procedure followed previous reports.[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.[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.[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.[17] At the end of the experiment, the length of each perfused intestinal segment was accurately measured.[25,26] Additionally, the pH of the collected samples was measured to verify that there was no pH change during the perfusion.

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

$$P_{eff} = \frac{-Q\,ln\,(C'_{out}/C'_{in})}{2\pi RL}$$

where Q is the perfusion buffer flow rate (0.2 mL/min), C'_{out}/C'_{in} is the ratio of the outlet and the inlet concentration of drug that has been adjusted for water transport,[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 strength 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[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.[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,[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 ≤ 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.

Table 1. Physiochemical Properties of Codeine Phosphate

Dosage Range	Up to 60 mg
Solubility	More than 120 mg/mL throughout the pH range of 1–7.5
log P	1.1
pKa	8.2
Ionization state	Base
log $D_{6.5}$	0.25
log $D_{7.5}$	0.6

Partition Coefficient

Codeine is a moderately lipophilic compound and has a log P value of 1.1 (octanol–water).[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).

p*K*a

Codeine is a weak base and has a pKa value of 8.2.[32]

PHARMACOKINETIC PROPERTIES

Absorption and BA

Codeine has a relatively low BA (50%),[1] which is likely because of the extensive first-pass effect rather than poor absorption. Indeed, codeine's human fraction of dose absorbed (F_{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.[33–36] Although no studies with radiolabeled codeine could be found in the literature to support F_{abs}, the high-cumulative urinary excretion of drug and drug-related material is a very strong evidence for F_{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.[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,[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[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.[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.[35] The apparent permeability (P_{app}) of codeine was 2.29×10^{-5} cm/s in the a→b direction and 1.99×10^{-5} cm/s in the b→a direction. In comparison, the P_{app}

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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.

of metoprolol, the benchmark for low/high permeability class boundary, was 1.77×10^{-5} cm/s in the a→b direction and 9.28×10^{-6} cm/s in the b→a direction. For further comparison, values for the low-permeability drug cimetidine were 1.64 and 8.58×10^{-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.[18–20] Similar permeability was revealed for codeine and metoprolol throughout the entire small intestine; codeine and metoprolol permeability values were 3.5×10^{-5} and 3.6×10^{-5} cm/s in the proximal jejunum, 7.8×10^{-5} and 7.2×10^{-5} cm/s in the middle small intestine, and 1.3×10^{-4} and 1.2×10^{-4} cm/s in the distal ileum, respectively (Table 2). These results corroborate the findings of Skolnik et al.[35] 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.[34,41] Codeine is extensively metabolized by the liver, predominantly to codeine-6-glucoronide, and in small part to norcodeine by CYP3A4.[34,42] A small fraction of codeine is converted by CYP2D6 to morphine, which is responsible for both the pharmacological activity and toxic effects of codeine.[34,41–44] Only about 3%–5% of codeine dose is excreted unchanged in the urine.[33,34,42] The elimination half-life of codeine was reported to be 1.8 h.[34] Quite variable clearance was reported in the literature, ranging from 40 to 140 L/h.[34,42,44–48]

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-t}, $AUC_{0-\infty}$, 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/anda/98/74–951_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-t}, $AUC_{0-\infty}$, 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-t}, $AUC_{0-\infty}$, 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/websiteresources/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 3. Excipients[a] Present in Codeine Phosphate IR Solid Oral Drug Products[b] 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)[c], and the Minimal and Maximal Amount of that Excipient Present per Dosage Unit in Solid Oral Drug Products with a MA in the US[d]

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

[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.

[b]Excluded are: combination products.

[c]Sources of data: CA, www.hc-sc.gc.ca (accessed 28-01-2014); CZ, www.sukl.cz/ (accessed 28-01-2014); DE, www.rote-liste.de; (accessed 29-01-2014); DK, www.dkma.dk (accessed 29-01-2014); ES, www.aemps.es (accessed 29-01-2014); FR, www.theriaque.org/; (accessed 29-01-2014); IE, www.imb.ie/ (accessed 04-02-2014); IS, www.serlyfjaskra.is (accessed 04-02-2014) NL, www.cbg-meb.nl. (accessed 05-02-2014); NO, www.legemiddelverket.no/ (accessed 05-02-2014); RO, www.anm.ro/ (accessed 05-02-2014); SE, www.lakemedelsverket.se (accessed 05-02-2014); SK, www.sukl.sk (accessed 05-02-2014); UK, www.medicines.org.uk/emc/ (accessed 10-02-2014).

[d]US: FDA's Inactive Ingredient Database, http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm (version date: September 16, 2013).

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

1. Codeine phosphate 15/−30/−60 mg tablets (Wockhardt UK Ltd.).
2. Codeisan 28.7 mg comprimidos.
3. CODEINE 15/−30 (codeine phosphate tablets, USP 15/−30 mg) (LABORATOIRES TRIANON INC.).
4. [N]ratio-CODEINE (codeine phosphate tablets USP 15/−30 mg) (Teva Canada Limited).
5. "Kodein" "Alternova," filmovertrukne tabletter.
6. Kodein "DAK," filmovertrukne tabletter.
7. PADERYL 19.5 mg CPR.
8. Kodein Recip 25 mg töflur.
9. Codeïnefosfaat 10/−15/−20 PCH, tabletten 10/−15/−20 mg.
10. Kodein 25 mg tabletter.
11. CODEINĂ FOSFORICĂ.
12. Kodein Recip 25 mg tabletter.
13. Codeinum phosphoricum Berlin–Chemie tabletten.
14. codi OPT® tabletten.
15. Tussoret® Tag-/Nacht–Kapseln.
16. Codein Slovakofarma 15/−30 mg.
17. Kodein "SAD," tabletter.
18. Codeină Fabiol 15 mg, comprimate.
19. FOSFAT DE CODEINĂ 15 mg comprimate.
20. Codein-SLOVAKOFARMA 15/−30 mg.
21. Codeinum phosphoricum Compren® 30 mg/-forte Compren® 50 mg tabletten.
22. Codipertussin mite tabletten codeinum phosphate 30 mg/codipertussin tabletten codeinum phosphate 50 mg.
23. Codant 30 mg tablets.
24. Codeïnefosfaat ratiopharm 10/−20 mg, tabletten.
25. CODEINĂ FOSFAT 15 mg comprimate.
26. CODEINĂ FOSFAT LPH 15 mg comprimate.
27. CODEINĂ FOSFAT MCC 15 mg comprimate.
28. CODEINE PHOSPHATE TABLETS BP 15/−30/−60 mg (Actavis UK Limited).

Table 4. Bioequivalence Study Results of Solid Oral Products Containing Codeine Phosphate

Strength on Which BE Performed	Subjects	Test Formulation Manufacturer or License Holder	Composition	Reference Product	Study Design	Prandial	Bioequivalence Criteria/ Statistics	Results	*In Vitro* Results
60 mg	24	Aspirin, butalbital, caffeine, and codeine (325/50/40/30 mg) produced by Jerome Stevens	Aspirin 325 mg Butalbital 50 mg Caffeine 40 mg Codeine phosphate 30 mg Excipients:starch, microcrystalline cellulose, talc, colloidal silicon dioxide, and stearic acid	Fiorinal (Sandoz Ltd.)	Open, two treatments, two periods crossover study	Fasting	90% CI (C_{max}, AUC_{0-t}, $AUC_{0-\alpha}$)	Bioequivalent	Dissolution in water exceeded 75% within 60 min for both products, as required by the USP
60 mg	24	Aspirin, butalbital, caffeine, and codeine (325/50/40/30 mg) produced by Endo pharmaceuticals	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	Fiorinal (Sandoz Ltd.)	Open, two treatments, two periods crossover study	Fasting	90% CI (C_{max}, AUC_{0-t}, $AUC_{0-\alpha}$)	Bioequivalent	Dissolution in water exceeded 75% within 60 min for both products, as required by the USP
12.8 mg	N/A	Ibuprofen and codeine (200/12.8 mg) produced by The Boots Company PLC, UK	Ibuprofen 200 mg Codeine phosphate 12.8 mg Excipients: microcrystalline cellulose, hypromellose, sodium starch glycolate, pregelatinised maize starch, titanium dioxide, and talc	Nurofen Plus (Crookes Healthcare Limited, UK)	A randomized, single dose, open-labeled two-period crossover study	Fasting	90% CI (C_{max}, AUC_{0-t}, $AUC_{0-\alpha}$)	Bioequivalent	N/A

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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.[33–36]

Codeine was previously classified as high-permeability drug in Caco-2 monolayers study.[35] 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.[35] 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.[17,36,49–51]

On the contrary, Kasim et al.[52] and Takagi et al.[53] 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),[23] 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,[52,53] pseudoephedrine,[23] and sotalol,[22] 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.,[35] 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.[54] 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 bioinequivalence 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[42]; however, the amount of codeine converted to morphine may be higher in UM by as much as 80-fold compared with EM.[10,15] For this reason, the CPIC Guidelines advise against the use of codeine in patients that were found to be UM by genetic screening.[11] 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 bioinequivalence 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* BE 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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