

Dissolution Specifications for Ibuprofen Soft Gelatin Capsules: A Proposal

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ABSTRACT

The aim of the present study was to propose a *Q* dissolution value as a quality control test for 400-mg ibuprofen soft gel capsules using the dissolution recommendations included in the FDA dissolution database. Two commercial batches of the reference product and two batches of three generic products were selected. Dissolution profiles were determined by using apparatus 1 at 150 rpm with 900 mL of phosphate buffer pH 7.2 as dissolution media. To determine the probability of passing the USP dissolution test, the R program with Burdick codes were used. Quality control tests including rupture time were also performed. Results showed that a *Q* dissolution value of 80% at 20 minutes could be recommended as a quality control test. A moderate correlation was found between rupture time and the percentage dissolved at 10 minutes.

KEYWORDS: Ibuprofen, soft gelatin capsules, release profiles, rupture test, dissolution

INTRODUCTION

Ibuprofen, the first member of propionic acid derivatives introduced in 1969, is the most frequently prescribed non-steroid anti-inflammatory drug (NSAID) because of its prominent analgesic and antipyretic role (1). Ibuprofen is highly soluble in 1-octanol, with a pKa value of 4.9 (2). The Ibuprofen biowaiver monograph describes it as Biopharmaceutical Classification System (BCS) class II active pharmaceutical ingredient (API), having high permeability and pH-dependent solubility with minimum solubility at pH 2 (3). The drug is supplied as tablets, oral suspension, capsules, and soft gelatin capsules, which is the preferred dosage form among adults due to its increased absorption rate, thereby reducing time for the expected effect (4). Several factors can influence release of the API from soft gelatin capsules, including physical properties of the gelatin shell, physical and chemical properties of the fill material, and moisture exchange between the shell and fill material (5, 6). Therefore, dissolution is an important test for drug product performance of this dosage form.

Currently there are dissolution requirements available for ibuprofen tablets and oral suspension (7, 8). Although the first liquid gel ibuprofen capsule was approved by the US

FDA in 1995, there is little information available about the dissolution characteristics of this dosage form. In the FDA dissolution method database, the recommendations for ibuprofen and ibuprofen potassium soft gelatin capsules are to use apparatus 1, at 150 rpm, and 50 mM phosphate buffer pH 7.2 as dissolution medium (9).

Considering that the dissolution test is an important tool to describe the performance characteristics of oral dosage forms and to ensure the batch-to-batch quality, the main objective of the present study was to evaluate the dissolution profiles of 400-mg ibuprofen soft gelatin formulations from the Mexican market and to propose a *Q* dissolution quality control acceptance criteria specification for this dosage form.

METHODS

Chemicals

Ibuprofen pharmaceutical secondary standard (purity 99.7%) was obtained from Sigma Aldrich, USA. Analytical grade monobasic sodium phosphate, sodium hydroxide, potassium hydroxide, anhydrous ethanol, phosphoric acid, and methanol were acquired from J.T.Baker. Water was obtained from a Milli-Q Reference (Millipore-Merck) system.

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Products

Products were selected according to their commercial availability. Two commercial batches of the Mexican reference product (Actron) and two commercial batches of three generic products containing 400-mg ibuprofen soft gelatin capsules were evaluated. All products were commercially available in Mexico and were randomly encoded as: R1 and R2 (reference product), A1, A2, B1, B2, C1, and C2 (generic products).

Quality Attributes

Physical attributes such as shape and color were carefully recorded for all the products.

Assay and uniformity of dosage units were evaluated as follows.

For assay sample preparation, 10 intact capsules were individually weighed to obtain their gross weights, taking care to preserve the identity of each capsule. Then the capsules were cut with a sharp open blade, the content was removed, and the emptied capsules were washed with methanol, allowing the solvent to evaporate at room temperature. The content of the 10 capsules was mixed and ibuprofen was determined by using United States Pharmacopoeia (USP) 43 method for ibuprofen tablets (7). The assay was performed by reverse-phase high-performance liquid chromatography (HPLC). The system used was a Shimadzu HPLC, which consisted of a dual plunger pump (LC-10 ATVP), a UV-Vis detector (SPD-10AVP) equipped with system controller (CBM-20A, UFLC), and an autoinjector (SIL-10A).

To assess uniformity of dosage units, the same sample preparation procedure used for assay was followed. Individual shells were weighted, and the net content of ibuprofen was calculated from the weight of content removed for the individual capsules and the result of the assay.

Rupture Test

A rupture test was carried out in accordance with the procedure described in *USP* General Chapter <2040> for the evaluation of soft gel capsules (10). The test was performed using six dosage units.

Preparation of Buffer Solution

Phosphate buffer pH 7.2 was prepared as dissolution medium according to *USP* requirements (11).

Dissolution Studies

Dissolution studies were conducted using *USP* apparatus 1 (Vankel 7000) at 150 rpm and 900 mL of phosphate buffer pH 7.2 as dissolution medium at 37 °C. Twelve

dosage units were evaluated for each product. Samples were taken at 5, 10, 15, 20, 30, and 45 min without medium replacement. In all cases, 5-mL samples were removed. Samples were filtered through a 35- μ m full flow filter (Agilent Technologies), diluted with the dissolution medium, and analyzed using a previously validated spectrophotometric method with dual beam UV at 222 nm.

The method was linear from 4–20 μ g/mL. The coefficients of variation for intra-day and inter-day measurements ranged from 0.5–2.4% and 1.3–2.8%, respectively. The percentage of relative error values did not exceed 1.1%, indicating that the method employed was precise and accurate. Furthermore, the method was selective because no interferences were found between the active drug, the excipients, or the color capsule shell of the products studied.

Data Analysis

Once the dissolution performance was evaluated, the probability of passing the *USP* dissolution test (*Q*) was estimated using the simulation approach proposed by Burdick et al. (12). The program codes written for the R environment were obtained from the book's website. The simulations were performed using R statistical software version 4.1.3. The codes allowed us to calculate the probability of each sample to pass the dissolution test in the two main stages and overall. The software also generated a heat map of probability data for the different batches studied. The correlation between rupture time and percentage of drug dissolved was calculated using the same software.

RESULTS AND DISCUSSION

Products and Quality Attributes

Table 1 shows the quality attributes of the products studied. Although differences in shape and color were observed between products, results from the assay test were satisfactory (93.9–101.4%). Additionally, all products met the acceptance criteria of uniformity of dosage units ($L1 \leq 15$).

In 2007, *USP* introduced the rupture test as a performance test for dietary supplements contained in soft-shell capsules. Although it is not a requirement for drug products, we conducted this test because it is a rapid and simple way for qualifying the film strength of soft gelatin capsules. Table 1 shows that rupture time was similar between batches and between the products R, A, and C, but batches of product B had the slowest rupture time and the highest variability within products.

Table 1. Physicochemical Characteristics of Ibuprofen Soft Gelatin Products

Product	Shape	Color	Assay, %	Uniformity of dosage units, % $L1 \leq 15$	Mean rupture time, min (range)
R1	Oval	Yellow	93.9	9.3	5.03 (3–6.5)
R2	Oval	Yellow	98.5	3.0	5.05 (4–6)
A1	Oblong	Red	97.3	4.9	6.23 (5.3–7.3)
A2	Oblong	Red	97.8	5.2	7.25 (3.5–10.2)
B1	Oblong	Purple	94.8	8.4	11.05 (8.2–14)
B2	Oblong	Purple	94.3	8.4	13.37 (10.3–17.4)
C1	Oblong	Pale Yellow	101.4	4.0	5.16 (3.3–8.3)
C2	Oblong	Pale Yellow	99.1	2.3	6.02 (3.4–9.4)

Dissolution Study

To date, there are no reports about the dissolution behavior of 400 mg ibuprofen soft gel capsules. The experimental conditions selected for the study were those proposed by the FDA; however, we included the sampling time at 15 min to determine if the products could meet the specification for very rapidly dissolving products. Figure 1 shows the mean dissolution profiles obtained. The dissolution method was able to differentiate between the products. Products R, A, and C met criteria for very rapid dissolution (i.e., 85% dissolved at 15 min), and both batches of product B met criteria for rapid dissolution (i.e., 85% dissolved at 30 min). The slow initial ascending phase in the dissolution profile for both batches of product B could be associated to the long rupture times, because a moderate correlation ($r = 0.7031$) was found between rupture time and the percentage dissolved at 10 min.

Specification Settings

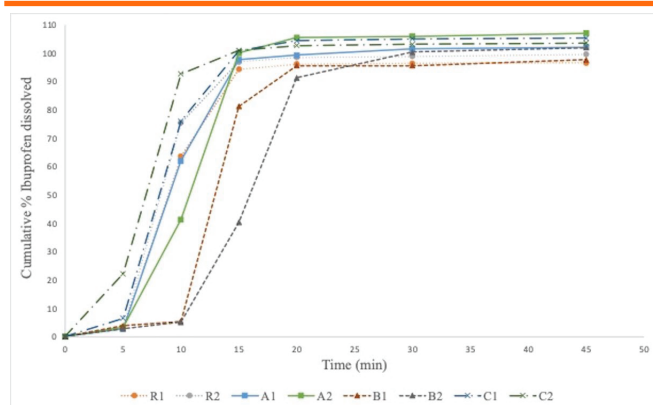


Figure 1. Mean dissolution profiles of different commercial products containing ibuprofen in soft gelatin capsules (400 mg) ($n = 12$).

Considering that ibuprofen soft gel capsules are generally more preferred by the consumers and that the dissolution profile is one of the critical quality attributes of a drug product, we propose a dissolution specification limit, defined by Q as a mean value at a given time point, that allows discrimination between acceptable and non-acceptable batches. Figure 2 shows the dissolution profile of each dosage unit evaluated from the different products and batches studied ($n = 12$ observations) using the FDA dissolution method. Differences were found in the percentage of API dissolved at 15 and 20 min. For 400-mg ibuprofen soft gel capsules, the Federal Commission for Protection Against Sanitary Risks (COFEPRIS) from Mexico requires a bioequivalence study for marketing approval. Because the products studied are commercially available, the 15-min time point could be overdiscriminating, so the 20-min time point was chosen.

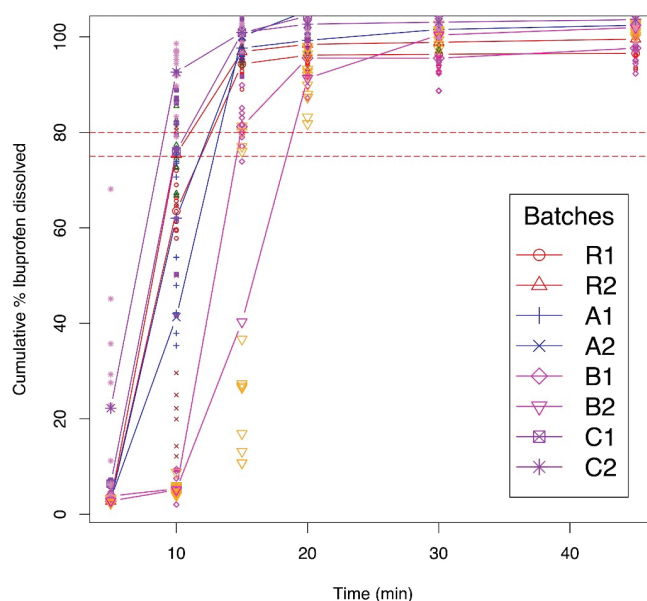


Figure 2. Dissolution profile of each dosage unit evaluated from the different products and batches of 400-mg ibuprofen soft gelatin capsules ($n = 12$).

To set the Q acceptance criteria specification, values of 75% and 80% were selected. As shown in Table 2, all the individual dissolution percentage values were above 80%, therefore a value of $Q = 80\%$ at 20 min is an adequate specification setting.

Considering the small number of batches evaluated and that the data showed a normal distribution, Burdick et al. R program codes (which use Monte Carlo techniques) were used to simulate data for Q . Simulations were performed with 10,000 random values of the mean and standard deviation of the batches studied (Table 2). The results

showed that most batches would pass in stage 1, except one batch from B product (46% of probability), which would be passing in stage 2 with a 100% of probability. The results indicate that the manufacturing process for product B (e.g., rupture time) could be improved to pass the USP stage 1 test.

Table 2. Probability to Pass USP Dissolution Test (Q = 80% at 20 min)

Product	Ibuprofen (%) Dissolved at 20 min Mean (SD) (n = 6)	Probability (%) to Pass Stage 1	Probability (%) to Pass Stage 1 or 2	Probability (%) to Pass Overall
R1	93.9 (0.90)	100	100	100
R2	96.9 (0.63)	100	100	100
A1	101.2 (1.14)	100	100	100
A2	108.2 (1.27)	100	100	100
B1	98.6 (1.90)	100	100	100
B2	91.0 (5.11)	45.7	100	100
C1	103.1 (1.55)	100	100	100
C2	102.5 (2.16)	100	100	100

CONCLUSIONS

The FDA-recommended dissolution method was able to differentiate between multiple brands of ibuprofen soft gelatin capsules. The rupture time might be an indicator of the variability of drug release for this dosage form. A Q dissolution value of 80% at 20 minutes could be recommended as a quality control test.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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