

# In Vitro Stability, Potency, and Dissolution of Duloxetine Enteric-Coated Pellets After Exposure to Applesauce, Apple Juice, and Chocolate Pudding

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## ABSTRACT

**Background:** Difficulty swallowing is a common problem in the clinical setting, particularly in elderly patients, and can significantly affect an individual's ability to maintain a proper level of nutrition.

**Objective:** The purpose of this in vitro study was to determine if mixing duloxetine enteric-coated pellets in food substances is an acceptable alternative method for administering this oral formulation to patients with swallowing difficulties.

**Methods:** To determine whether administration in food substances with varying pH values (applesauce and apple juice, pH = ~3.5; chocolate pudding, pH = ~5.5–6.0) affects the enteric coating of the formulation, duloxetine pellets (ie, the contents of a 20-mg duloxetine capsule) were exposed to applesauce, apple juice, and chocolate pudding at room temperature and tested in triplicate for potency and impurities; for dissolution, 6 replicates were tested. To assess product stability and integrity of the enteric coating, potency, impurities, and dissolution tests of the pellets were conducted and compared with pellets not exposed to food. The duloxetine pellets were extracted from the food material using a solution of 0.1 normal (N) hydrochloric acid (HCl) prepared from concentrated HCl (commercially available) and deionized water. For the potency and impurities tests, a 40:60 solution of acetonitrile and pH 8.0 phosphate buffer was used as the sample solvent to extract the active pharmaceutical ingredient from the formulation to prepare the samples for testing. The amount of active pharmaceutical ingredient released (in vitro dissolution) from the pellets after exposure to the food substances was determined using 2 media solutions, 0.1 N HCl followed by pH 6.8 phosphate buffer. Applesauce and chocolate pudding were selected as vehicles for oral administration, while apple juice was intended to be used as a wash for a nasogastric tube.

**Results:** Mean (SD) potency results for the 20-mg capsule strength were 20.256 (0.066), 20.222 (0.163), and 19.961 (0.668) mg/capsule for the comparator not exposed to food, the sample exposed to applesauce, and the sample exposed to apple juice, respectively. However, exposure to chocolate pudding altered the integrity of the pellet's enteric coating (mean [SD] potency results, 17.780 [1.605] mg/capsule). Results of impurities testing suggested that none of the test foods caused significant degradation of the drug product. Mean dissolution results found that after 2 hours in 0.1 N HCl,  $\leq 1\%$  of duloxetine was released from the comparator and pellets exposed to applesauce and apple juice. However, the mean dissolution profile of the sample exposed to pudding reported near-total release (90%) after 2 hours in 0.1 N HCl during the gastric challenge portion of the dissolution test.

**Conclusions:** Results from this study found that the enteric coating of duloxetine pellets mixed with applesauce or apple juice was not negatively affected. The pellets were stable at room temperature for  $\leq 2$  hours and should quantitatively allow delivery of the full capsule dose, provided that the pellet integrity is maintained (ie, not crushed, chewed, or otherwise broken). Therefore, mixing duloxetine pellets with applesauce or apple juice appears to be an acceptable vehicle for administration. However, exposing the pellets to chocolate pudding damaged the pellets' enteric coating, suggesting that pudding may be an unacceptable vehicle for administration. (*Clin Ther.* 2008;30:1300–1308) © 2008 Excerpta Medica Inc.

**Key words:** food exposure, Cymbalta, duloxetine hydrochloride, antidepressant, SNRI, drug stability.

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## INTRODUCTION

Swallowing difficulties are common in the clinical setting, particularly in elderly patients, and can significantly affect an individual's ability to maintain a proper level of nutrition.<sup>1</sup> Administration of oral medications in patients who have swallowing problems and are using feeding tubes can be problematic. Care must be taken to avoid compromising the properties of the drug formulation (enteric coating, controlled release, long acting, or extended release), which could lead to incorrect administration by delivering less-than-therapeutic doses or quick release of high doses.<sup>2</sup>

Duloxetine hydrochloride\* is a selective serotonin-norepinephrine reuptake inhibitor currently indicated in the United States for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia.<sup>3</sup> The prescribing information for duloxetine hydrochloride delayed-release capsules states that the capsules should be swallowed whole and not chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids, as all these actions may affect the enteric coating.<sup>3</sup> However, because administering oral medications to patients with swallowing difficulties is a challenging patient care issue,<sup>1,2</sup> identifying appropriate foods that will not compromise or damage the duloxetine formulation may be helpful information for health care professionals. The goal of this *in vitro* study, therefore, was to explore the feasibility of mixing the duloxetine enteric-coated pellets with food substances to facilitate administration in these difficult-to-treat patients.

Duloxetine hydrochloride is unstable and degrades rapidly (~15% per hour) when exposed to acidic conditions (data on file, US New Drug Application [NDA] 21-427, Eli Lilly and Company, Indianapolis, Indiana, November 2001). Consequently, the finished pharmaceutical dosage form is a gelatin capsule containing enteric-coated pellets. The pellets' enteric coating was designed to dissolve at a pH of ~5.5; thus, the enteric coating protects the active pharmaceutical ingredient (API) from degradation in the stomach. Also, using pellets as a dosage form aids transit of the API through the stomach

into the higher pH regions of the gastrointestinal tract, where the API is released and absorbed.

This study involved exposing duloxetine enteric-coated pellets to food substances with varying pH values for a specified amount of time. After exposure to food, the pellets were immediately evaluated for potency, impurities, and rate of release (dissolution). All methods used comply with International Conference on Harmonisation standards designed for this type of study.<sup>4,5</sup>

## MATERIALS AND METHODS

This *in vitro* study encompassed potency and impurities tests and the dissolution test. The potency test was designed to confirm the strength and identity of the API, and the impurities test was designed to determine the amount of relevant process impurities and/or potential degradation products. The goal of the dissolution test was to evaluate the integrity of the enteric coating.

### Materials

The test food materials were applesauce (Mott's® [Mott's Inc., Rye Brook, New York] original applesauce in 6 individual 4-ounce serving cups; pH = ~3.5), chocolate pudding (Kraft® Handi-Snacks [Kraft Foods Global, Inc., Northfield, Illinois] chocolate pudding in 4 individual 3.5-ounce serving cups; pH = ~5.5–6.0), and apple juice (Mott's® 100% apple juice in a 32-fluid ounce [1-quart] plastic bottle; pH = ~3.5). They were chosen because they are usually available in a clinical setting in the United States and because of their utility of administration. The applesauce and pudding were intended as potential vehicles for oral administration, while the apple juice was intended as a wash for a nasogastric tube. Applesauce and apple juice contain citric acid and therefore have a more acidic pH, while pudding is a dairy product with a more neutral pH. The foods chosen for this study have pH values at or below the level where the enteric coating is designed to dissolve and release the API (ie, a pH of ~5.5).

Dissolution testing involves assessing the drug under conditions that are similar, but not equivalent, to those in the stomach. Duloxetine stability data for the *in vitro* dissolution test suggest that drug release in the gastric challenge portion of dissolution testing (2 hours in a solution of 0.1 normal [N] hydrochloric acid [HCl] prepared from concentrated HCl [commercially

\*Trademark: Cymbalta® (Eli Lilly and Company, Indianapolis, Indiana).

available] and deionized water) is the highest with the lowest marketed dosage strength of duloxetine, 20 mg (data on file, US NDA 21-427). Thus, the enteric coating prevents early release of the API (duloxetine); however, there is a small amount (~1%–2%) of residual API that is outside of the enteric coating and, typically, the largest amount released (relative to the capsule strength) is observed for the 20-mg capsule strength. Therefore, a representative batch of 20-mg duloxetine capsules (currently the lowest marketed dosage strength)<sup>3</sup> was tested because it should provide the largest amount of drug released in the dissolution test. The finished pharmaceutical dosage forms of duloxetine capsules (20-mg strength), along with the respective reference standard (duloxetine hydrochloride), were used.

The duloxetine pellets were extracted from the food material using the 0.1 N HCl solution. This solution was chosen because duloxetine stability data have suggested that the enteric coating remains intact for exposure times of  $\geq 2$  hours in 0.1 N HCl (data on file, US NDA 21-427). For the potency and impurities tests, a 40:60 solution of acetonitrile and pH 8.0 phosphate buffer was chosen as the sample solvent to extract the API from the formulation to prepare the samples for testing.

The amount of API released (in vitro dissolution) from the pellets after exposure to the food substances was determined using 2 media solutions, 0.1 N HCl followed by pH 6.8 phosphate buffer, in accordance with *United States Pharmacopeia (USP) 26* methods for delayed-release (enteric-coated) articles.<sup>6</sup>

## Procedures

### Potency and Impurities Tests

A measured amount of each food material to be used (~30 mL [2 tablespoons]) was placed into a glass beaker, and the contents of a 20-mg duloxetine capsule were emptied onto the test food, taking care not to crush the pellets, which would have damaged and compromised the integrity of their enteric coating. The food and pellets were mixed with a plastic stirring rod to immerse all pellets into the food. After the pellets were mixed into the food, a stopwatch was used to measure exposure time. An equal amount of placebo pellets (manufactured by Eli Lilly and Company) corresponding to a 20-mg capsule strength was prepared in the same manner to check for chromatographic interferences. All samples were prepared in

triplicate for each of the 3 test foods, and each sample replicate was tested once. After the set exposure time (30 minutes for the pudding, 2 hours each for the applesauce and apple juice), the pellets were rinsed from the test food by submerging the food and pellets in 0.1 N HCl. The food material was removed from the pellets by successive decanting and rinsing with 0.1 N HCl to minimize testing interference. Any remaining 0.1 N HCl was removed by decanting, and the pellets were transferred to the appropriate container by rinsing with the sample solvent (40:60 acetonitrile and pH 8.0 phosphate buffer). In addition, for comparison purposes, a 20-mg duloxetine capsule and an equal amount of placebo pellets corresponding to a 20-mg capsule strength were prepared in triplicate with no exposure to food.

The pellets were carefully extracted from the test food to minimize exposure to the acidic medium (0.1 N HCl). This was done because exposure of the pellets to 0.1 N HCl should not compromise the integrity of the enteric coating. However, if the enteric coating was compromised as a result of exposure to the test foods, any degradation would be minimal since the exposure time was not long enough to allow significant degradation. Immediately after extraction, samples were prepared at a concentration of 0.1 mg/mL in the sample solvent (40:60 acetonitrile and pH 8.0 phosphate buffer). The sample solvent was designed to extract the API without degradation, and the buffered pH of the sample solvent should absorb any residual 0.1 N HCl without significantly lowering the pH. The samples were compared against duplicate reference standards of duloxetine hydrochloride prepared at a concentration of 0.1 mg/mL as the free base in the sample solvent (40:60 acetonitrile and pH 8.0 phosphate buffer). Standards and samples for both potency and impurities were refrigerated (~5°C) before injection while in the autosampler. The analysis was done using isocratic reverse-phase high-pressure liquid chromatography (HPLC) with single-wavelength ultraviolet (UV) detection at 230 nm. The mobile-phase composition was 58.7% 25-mM phosphate buffer with 1.5% triethylamine at pH 5.5, 32.3% methanol, and 9.0% tetrahydrofuran. The analytical column, an ACE® C8 (Advanced Chromatography Technologies [ACT], Aberdeen, United Kingdom; 7.5-cm length  $\times$  4.6-mm inside diameter; 3- $\mu$ m particle size), was kept at ~40°C at a flow rate of 1.5 mL/min. The sample and standard injection volume was 10  $\mu$ L.

Duloxetine peak area response was used for quantitation. Potency was measured against the known concentration of the standard curve while impurities were calculated on an area percent basis (peak area vs total area = area of a given peak/total area of all peaks  $\times$  100). Chromatograms of the representative standard and sample are shown in Figure 1.

### Dissolution Test

Samples were prepared in the test foods in the same manner described for the potency and impurities tests, except 6 replicates were prepared in each test food (each replicate was tested once). The dissolution samples were tested in accordance with *USP 26* methods for delayed-release (enteric-coated) articles.<sup>6</sup> After extraction of the pellets with 0.1 N HCl, each sample replicate was placed into separate dissolution baskets. The baskets were then attached to the spindles of the dissolution bath and lowered into 1000 mL of the 0.1 N HCl medium at 37°C and rotated at 100 rpm for 2 hours. A sample aliquot was taken from each vessel at 2 hours, and the baskets were removed from the 0.1 N HCl medium and immediately attached to the spindles on a second dissolution bath; they were

then lowered into 1000 mL of the pH 6.8 phosphate medium (a 3:1 ratio of 0.1 N HCl to 0.20 M tribasic sodium phosphate) at 37°C and rotated at 100 rpm for 1 hour. Sample aliquots were taken from each vessel at 15-minute intervals. Two sets of duplicate standards were prepared in pH 6.8 phosphate buffer; one set was prepared at 2  $\mu$ g/mL for the samples in 0.1 N HCl and one set at 20  $\mu$ g/mL for the samples in pH 6.8 phosphate buffer. Standards and samples were analyzed using isocratic reverse-phase HPLC with single-wavelength UV detection at 230 nm. The mobile-phase composition was 58.7% 25-mM phosphate buffer with 1.5% triethylamine at pH 5.5, 32.3% methanol, and 9.0% tetrahydrofuran. The analytical column used was an ACT ACE C8 (7.5-cm length  $\times$  4.6-mm inside diameter; 3- $\mu$ m particle size) and was kept at  $\sim$ 40°C at a flow rate of 1.5 mL/min. The sample and standard injection volume was 10  $\mu$ L. Duloxetine peak area response was used for quantitation and measured against the known concentration of the standard curve for samples in the pH 6.8 phosphate medium. For samples in the 0.1 N HCl medium, degradation of the samples was accounted for through the quantitation of not only the duloxetine peak but

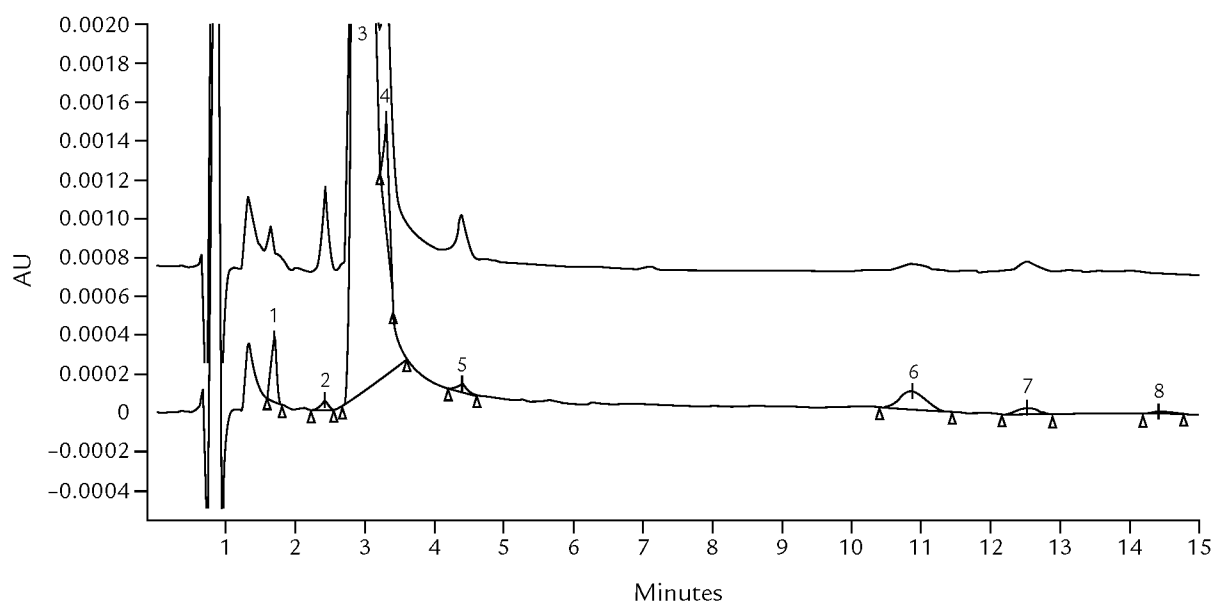


Figure 1. Overlay of chromatograms of the representative standard (top) and the representative sample (bottom). Peak key: 1 = unknown impurity; 2 = unknown impurity; 3 = duloxetine (active pharmaceutical ingredient); 4 = 3-isomer of duloxetine; 5 = 1-naphthol; 6 = *N*-formyl duloxetine; 7 = unknown impurity; 8 = unknown impurity. Scale: 1 volt = 1 absorbance unit (AU).

also a second known impurity peak (1-naphthol) and the application of a response factor to the 1-naphthol peak area response. The duloxetine peak area and the corrected 1-naphthol peak area responses were then added to calculate the amount of duloxetine released. Because duloxetine degrades rapidly in 0.1 N HCl, a method was needed to determine the amount of duloxetine released. A linear relationship between the loss of duloxetine and the formation of 1-naphthol, a duloxetine degradation product, was identified. Consequently, 1-naphthol was used as a surrogate for duloxetine released in 0.1 N HCl. The peak area increase in 1-naphthol was multiplied by 2.06 to obtain the peak area for duloxetine that would have resulted had duloxetine not degraded. Thus, the 1-naphthol peak was integrated and the resulting area multiplied by 2.06 before adding it to the peak area of duloxetine detected. By comparison to the area response of the external duloxetine standard, the summed area was used to calculate the amount of duloxetine released (data on file, US NDA 21-427).

Because the chocolate pudding has a more neutral pH (~5.5–6.0), closer to that at which the enteric coating is designed to dissolve (~5.5), the duloxetine pellets were exposed to the pudding for less time (30 minutes instead of 2 hours) to reflect a practical amount of time for preparation and administration in a clinical setting. The pellets were exposed to both the applesauce and apple juice for 2 hours because the apparent pH of both these items (~3.5) is well below the threshold for the dissolution of the enteric coating (data on file, US NDA 21-427).

### Results Criteria

The duloxetine pellets were exposed to food and compared with a nominal sample preparation. Data were considered acceptable if the results fell within the current specifications for each test, as follows: for potency,  $\geq 90\%$  and  $\leq 110\%$  of the labeled amount of duloxetine (20 mg,  $\pm 2$  mg); for purity, total degradation products had to be  $\leq 0.6\%$ , calculated as peak area versus total area (area of a given peak/total area of all peaks  $\times 100$ ). For dissolution, no individual sample could exceed 10% released (relative to the dose strength) after 2 hours in the acidic medium and quantity = 75% released (cumulative relative to the dose strength) after 1 hour in the phosphate buffer medium.

## RESULTS

The mean (SD) potency results were within  $\pm 2\%$  of the theoretical label claim of 20 mg/capsule and were within the established specification range for samples exposed to applesauce (20.222 [0.163] mg/capsule) and apple juice (19.961 [0.688] mg/capsule). However, for the sample exposed to chocolate pudding, the mean (SD) potency results were  $>10\%$  below the theoretical label claim (17.780 [1.605] mg/capsule) (Table I).

The impurities present in the samples exposed to each food material were comparable with the 20-mg duloxetine capsule not exposed to food (Table II). In addition, the chromatography of the placebo samples (excipients only) exposed to food found no significant or additional peaks compared with a normal placebo sample not exposed to food (Figure 2). These results imply that none of the test foods caused significant interference or bias in the quantification of results for any of the tests.

The mean results from the dissolution testing are presented in Table III and Figure 3. Each successive time point represents the cumulative sum of duloxetine released. For example, at 15 minutes in pH 6.8 phosphate buffer for the sample exposed to pudding, ~10% of duloxetine was released in the buffer (90% released in the 0.1 N HCl), but the reported value is the total release in the buffer and the acid (100%). The mean dissolution profiles of duloxetine pellets exposed to applesauce and apple juice were similar to the mean dissolution profile of the 20-mg duloxetine capsule, which was not exposed to food (Table III, Figure 3). However, the mean dissolution profile of the sample exposed to pudding reported near-total release (90%) after 2 hours in 0.1 N HCl, indicating that the 30-minute exposure to pudding had negatively affected the integrity of the enteric coating due to the pudding's elevated pH.

## DISCUSSION

Results of all testing (potency, impurities, and dissolution) suggest that applesauce and apple juice did not negatively affect the performance or integrity of the enteric-coated duloxetine pellets for the exposure times that were tested (2 hours each). However, results of dissolution and potency testing suggest that exposure of duloxetine pellets to chocolate pudding (exposure time, 30 minutes) negatively affected the performance and integrity of the enteric coating due to the pudding's

Table I. Results of potency testing of duloxetine enteric-coated pellets. Three replicates were tested.

| Replicate | Duloxetine Sample Not Exposed to Food |                 | Duloxetine Sample Exposed to Mott's®* Applesauce, 2 h |                | Duloxetine Sample Exposed to Mott's®* Apple Juice, 2 h |                | Duloxetine Sample Exposed to Kraft®† Handi-Snacks Chocolate Pudding, 30 min |                |
|-----------|---------------------------------------|-----------------|---|----------------|--|----------------|---|----------------|
|           | Label Claim, mg/capsule‡              | Label Claim, %§ | Label Claim, mg/capsule                               | Label Claim, % | Label Claim, mg/capsule                                | Label Claim, % | Label Claim, mg/capsule   | Label Claim, % |
| 1         | 20.182                                | 100.911         | 20.396  | 101.981        | 20.332   | 101.662        | 18.730  | 93.648         |
| 2         | 20.308                                | 101.539         | 20.195  | 100.977        | 19.191   | 95.954         | 15.927  | 79.634         |
| 3         | 20.279                                | 101.397         | 20.073  | 100.365        | 20.361   | 101.806        | 18.685  | 93.424         |
| Mean      | 20.256                                | 101.282         | 20.222  | 101.108        | 19.961   | 99.807         | 17.780  | 88.902         |
| SD        | 0.066                                 | 0.329           | 0.163   | 0.816          | 0.668  | 3.338          | 1.605   | 8.027          |

\* Registered trademark of Mott's Inc., Rye Brook, New York.

† Registered trademark of Kraft Foods Global, Inc., Northfield, Illinois.

‡ Label claim is the calculated amount in milligrams per capsule; the theoretical label claim is 20 mg/capsule.

§ Percentage label claim = calculated label claim/theoretical label claim × 100.

elevated pH. Consequently, chocolate pudding and any other food with a similar pH (ie, ~5.5–6.0), or a higher apparent pH, are unacceptable food vehicles for administering duloxetine enteric-coated pellets to patients.

Results of the dissolution testing of the duloxetine samples exposed to applesauce and apple juice were

similar compared with a 20-mg duloxetine capsule not exposed to food. In addition, exposure of duloxetine enteric-coated pellets to applesauce or apple juice for ≤2 hours found no apparent effect on the product stability or performance of the intact pellets. These findings suggest that the enteric-coated duloxetine

Table II. Results of impurities testing for duloxetine enteric-coated pellets. Three replicates were tested.

| Replicate | Percentage of Total Impurities (Peak Area vs Total Area)* |  |   |   |
|-----------|---|--|---|---|
|           | Duloxetine Sample Not Exposed to Food                     | Duloxetine Sample Exposed to Mott's®† Applesauce | Duloxetine Sample Exposed to Mott's®† Apple Juice | Duloxetine Sample Exposed to Kraft®‡ Handi-Snacks Chocolate Pudding |
| 1         | 0.1150  | 0.0680   | 0.0737  | 0.0776  |
| 2         | 0.1029  | 0.0702   | 0.0727  | 0.0907  |
| 3         | 0.1214  | 0.0671   | 0.0793  | 0.0835  |
| Mean      | 0.1131  | 0.0684   | 0.0752  | 0.0839  |
| SD        | 0.0094  | 0.0016   | 0.0036  | 0.0066  |

\* For individual impurities, peak area versus total area = area of a given peak/total area of all peaks × 100. Total impurities = the sum of the individual impurities.

† Registered trademark of Mott's Inc., Rye Brook, New York.

‡ Registered trademark of Kraft Foods Global, Inc., Northfield, Illinois.

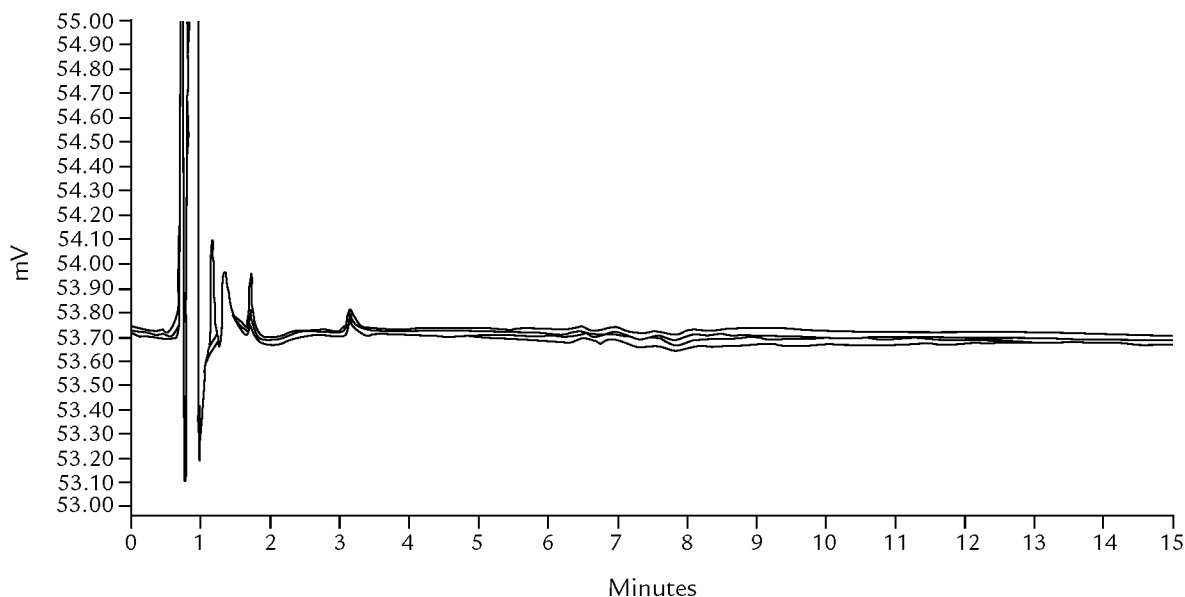


Figure 2. Chromatographic overlay of placebo samples exposed to each food compared with the placebo sample not exposed to food. mV = millivolt.

Table III. Results of mean dissolution testing of duloxetine enteric-coated pellets. Six replicates were tested.

| Sample                                      | Amount of Duloxetine Released<br>(% [Mean of 6 Replicates]) |                      |                         |                      |                      |
|---|---|----------------------|-------------------------|----------------------|----------------------|
|   | 0.1 N HCl<br>(Gastric<br>Challenge)                         |                      | pH 6.8 Phosphate Buffer |                      |                      |
|   | 2 h<br>(120 min)*   | 15 min<br>(135 min)* | 30 min<br>(150 min)*    | 45 min<br>(165 min)* | 60 min<br>(180 min)* |
| Duloxetine 20-mg capsule†                   | 1   | 50                   | 80                      | 93                   | 98                   |
| Mott's®‡ applesauce§                        | 0   | 50                   | 85                      | 98                   | 101                  |
| Mott's®‡ apple juice§                       | 0   | 44                   | 84                      | 96                   | 99                   |
| Kraft®   Handi-Snacks chocolate<br>pudding¶ | 90  | 100                  | 104                     | 104                  | 105                  |

0.1 N HCl = 0.1 normal hydrochloric acid.

\*For each successive time point, this was the total cumulative time in minutes.

† Sample not exposed to food; dissolution test performed (2 hours in acidic solution, 1 hour in buffer solution).

‡ Registered trademark of Mott's Inc., Rye Brook, New York.

§ Sample exposed to applesauce or apple juice for 2 hours, then dissolution test performed (2 hours in acidic solution, 1 hour in buffer solution).

|| Registered trademark of Kraft Foods Global, Inc., Northfield, Illinois.

¶ Sample exposed to pudding for 30 minutes, then dissolution test performed (2 hours in acidic solution, 1 hour in buffer solution).

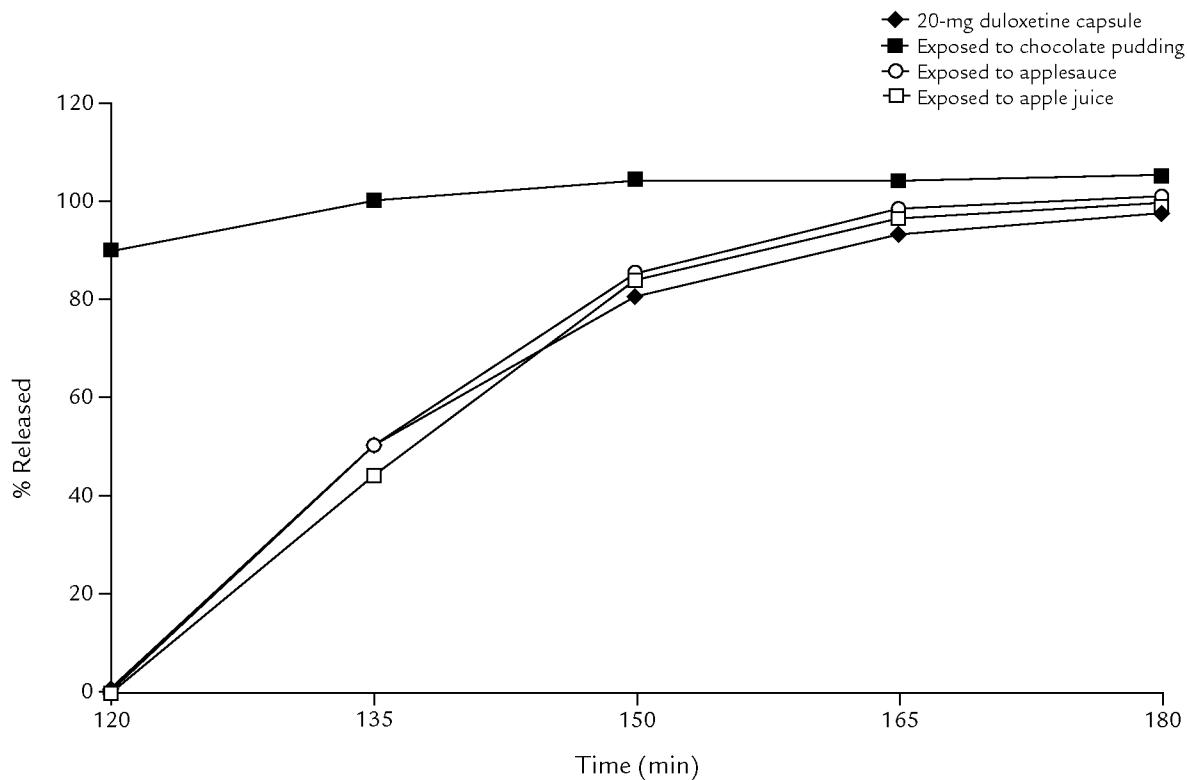


Figure 3. Overlay of dissolution profiles of duloxetine samples exposed to foods with varying pH. Note: 120 minutes is the starting point and is the level after 2 hours in acidic media.

pellets should remain stable for up to 2 hours at room temperature when mixed with applesauce or apple juice (apparent pH value, ~3.5 [for each]) and quantitatively allow delivery of the full capsule dose, provided that the pellet integrity is maintained (ie, pellets are not crushed, chewed, or otherwise broken).

The findings from this in vitro study should be interpreted with some caution. Although the duloxetine pellets were not affected after 2 hours' exposure to apple juice, the study did not investigate administering duloxetine via a nasogastric tube. Therefore, additional study exploring this route of administration is needed. Also, the study results are not sufficient to support a change in language in the duloxetine prescribing information. Further testing in a clinical setting is required to evaluate the bioavailability, efficacy, and safety of duloxetine administered in food or juice.

## CONCLUSIONS

This study found that the exposure of duloxetine pellets to acidic foods (ie, applesauce, apple juice) for

≤2 hours at room temperature did not negatively affect the integrity of the enteric coating or the stability of duloxetine. However, the exposure of duloxetine pellets to a less acidic food (ie, chocolate pudding) negatively affected the enteric coating, suggesting that pudding may be an unacceptable vehicle for administration.

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