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Research

# Rapid and Fast-Release Acetaminophen Gelcaps Dissolve Slower Than Acetaminophen Tablets

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## Abstract

The dissolution properties of oral medicinal drugs are affected by formulation and used to market over-the-counter medications. Acetaminophen is one of the most commonly used over-the-counter pain and fever-reducing medications with an estimated global yearly market value of over $350 million US dollars [1]. Acetominophen gelcaps are, in general, sold at higher prices than company-matched standard tablets. Standard acetaminophen tablets and rapid or fast-release gelcaps from five major US companies were analyzed using the industry standard test for dissolution. Results indicate that acetaminophen gelcaps marketed as rapid or fast-release are slower acting under *in vitro* dissolution conditions compared to the company-matched tablet dose.

**Keywords:** dissolution; acetaminophen; rapid release; fast-release; quick release; standard release; medication release; over-the-counter; generic drugs.

## Introduction

The release of active ingredients from drug products is an essential component of pharmacokinetics of absorption, distribution, metabolism, and excretion that influences onset of drug action after oral administration. Following the widely accepted standard set by the United States Pharmacopeia (USP) for *in vitro* drug release rate, or dissolution analysis, we investigated rapid (or fast) release medications from five major US companies (Rite Aid, Walgreens, CVS, Johnson & Johnson Tylenol, and Walmart Equate) selling acetaminophen, also called paracetamol or N-acetyl-para-aminophenol, compared to company-matched tablets that do not have claims of rapid or fast-release characteristics.

The specific formulation of individual drug products including excipients, binders, and sustained release materials is propriety knowledge. Many companies sell over-the-counter drug products in multiple forms including those advertised as “fast-release,” or “rapid release”. Modified release drug products can control the pharmacokinetic and pharmacodynamic properties of drug administration, which is also applicable to extended release forms [2]. The *in vitro* release of drugs into solution over time is studied for solid oral drug dosages with dissolution testing. Dissolution testing is commonly used in the pharmaceutical industry to test the quality and effectiveness of drug release from solid oral medications.

Formulating pure medicinal drugs for oral delivery requires non-active ingredients that affect dissolution properties [3]. These

excipients may include any of a wide variety of regulated substances including sugars, cellulose, magnesium stearate, starch, talc, and polyethylene glycols that bind the active ingredient of an individual drug dose in solid form from mixed powders following mold-based processing [4]. Excipients can comprise 90% of a medication's mass depending on the drug type [5]. Additionally, many solid oral drug products are coated with non-active ingredients that may regulate dissolution [6]. Coatings may range in thickness of gelatin or other polymer-based material that have a pronounced effect on dissolution in viscous solutions [7]. Generally, polymer coatings may help to shield the taste of medication, allow for recognition by color, and/or aid in the comfort of swallowing [8]. In the case of acetaminophen, coated capsule-shaped tablets, or caplets, are commonly marketed as gelcaps.

Acetaminophen is included on the World Health Organization List of Essential Medicines and is the most commonly used medication for fever reduction and pain mitigation in the US and Europe [9,10]. Acetaminophen can be purchased over-the-counter in many forms including tablet, caplet, capsule, gelcap, and liquid suspension and is typically dosed in 325 mg, 500 mg, or 650 mg solid forms. As a Biopharmaceutical Classification System type III drug, acetaminophen bioavailability is limited by permeation rate and not solubility. Therefore, *in vitro* dissolution studies are considered safe determinants of bioequivalence for acetaminophen formulation [11].

Acetaminophen medications are manufactured and distributed through a variety of marketplaces. Post manufactured products are marketed for sale online or in person with proprietary labelling containing drug identity and dosage amount. All commercial drugs are tracked through unique lot numbers assigned by manufacturers to each individual lot or batch of the medication. Additionally, a National Drug Code (NDC) is commonly included on US medication labelling. The NDC Directory is maintained by the FDA and used to identify the pharmaceutical establishment that manufactured or processed the drug for commercial distribution (see Section 510 of the Federal Food, Drug, and Cosmetic Act) [12]. Knowing the authenticity of medications does not guarantee the measure of quality or consistency between individual lots of medication. In the case of acetaminophen, the claims for rapid or fast-release products have been scrutinized previously [13]. Our work provides a thorough comparison of five of the top acetaminophen branded and generic products marketed and sold in the US.

Given wide-spread use of over-the-counter and prescription medications, the quality and value of medications are an important public health, consumer safety, and economic concern.

## Methods

For this study, all acetaminophen samples were purchased from pharmacies as over-the-counter medications in the United States New York Tri-State Area. Medications were rejected if the time of testing was within a year of the labelled expiration date. Medications with 100 dosage units at a concentration of 500 mg were purchased. Standard release tablets (herein tablets) and rapid-release or fast-release gelatin coated tablets (herein gelcaps) sold by five companies and from five lots per company were tested. Companies were chosen to represent the top branded version of acetaminophen [14] and the top 4 retail pharmacy chains selling their own generic acetaminophen products [15]. Companies were Rite Aid (company #1), Walgreens (company #2), CVS (company #3), Johnson & Johnson Tylenol (company #4), and Walmart Equate (company #5). Six tablets and six gelcaps from a single company were tested together alternating through companies until each lot from each company of either tablets or gelcaps were tested twenty-four times. In total, 1,200 units of medication were tested in the primary study controlling for variables within and between companies' lots to determine differences in dissolution rates between tablets and gelcaps.

| Primary Study Variable | Companies | Lots per Company | Units tested per Lot | Total |
|---|---|---|---|---|
| Tablets | 5 | 5 | 24 | 600 |
| Rapid or Fast-Release Gelcaps | 5 | 5 | 24 | 600 |

**Table 1:** Experimental Design. This study compares dissolution between 500 mg acetaminophen tablets and gelcaps controlling for variability in tests, lots, and between major companies in the United States.

Two follow-up studies were performed. First, additional rapid or fast-release tablets without coating were purchased from company #3, which, after reasonable search of retail pharmacies in the New York Tri-State Area, appeared to be the only company evaluated that markets additional rapid-release acetaminophen products beyond gelcaps. These were analyzed side-by-side with gelcaps and standard-release tablets of the company #3. Furthermore, 100 additional gelcaps sampled from all twenty-five study lots were analyzed following the removal of their coating (four gelcaps from each lot).

## Dissolution Testing

Dissolution tests were performed in accordance with the United States Pharmacopeia (USP) standard for dissolution [16] and monograph for acetaminophen tablets, a common test between medications labelled tablet or gelcap. Dissolution Tester RC-6 (Tianjin Guoming Medicinal Equipment) instruments that hold six test vessels each were used with testing apparatus II (paddle type). The temperature and pH of dissolution buffer was verified using a dual probe calibrated and certified to ISO 17025:2005 standards (Mettler Toledo).

Dissolution was performed at 50 rpm paddle speed and 37.5 ± 0.1°C using 900 ml of dissolution buffer: 50 mM monobasic potassium phosphate (KH2PO4, 99% ACS Reagent, Sigma-Aldrich) and sodium hydroxide (NaOH, Sigma-Aldrich) to reach pH 5.8 at 37.5°C in deionized water. Although the USP monograph only requires one sampling at the 30-minute time point, greater resolution is needed to evaluate release claims in acetaminophen. For this study, samples were collected every 120 ± 2 seconds for a total of 30 minutes, which enabled sufficient resolution to ascertain differences in acetaminophen products. 0.5 ml samples were aspirated from 50% vessel depth and greater than 2 cm from the vessel wall and filtered using 0.45 µm PVDF membrane (Denville Scientific) to remove undissolved acetaminophen and particulate excipients. Full dissolution was verified for all medication by comparison to a standard curve prepared using reference standard acetaminophen (Sigma-Aldrich, data not shown). To control for potential variability in vessel position, crossover methodology was used where tablets and gelcap's were tested side-by-side in alternating order and tests alternated between tablet or gelcap in the first vessel position. The results of *in vitro* dissolution are shown in Figures 1 and 2.

For analysis of gelcaps with their coating removed, the gelatin coating was manually removed from the inner tablet and all components were added to the dissolution vessel at time zero of sample collection (see Figure 3). Results are shown in Figure 4.

## UV Analysis

Samples were analyzed for ultraviolet light or UV absorbance at 243 nm corresponding to the peak absorbance of acetaminophen using an Epoch microplate spectrophotometer (BioTek). Samples were consistently diluted in an appropriate amount of dissolution buffer to reach the working range of the spectrophotometer. Greiner UV-Star 96-well plates were used for sample measurement. Prior to sample analysis, the optical interference at 243 nm for UV-Star plates was tested side-by-side with quartz and determined negligible (data not shown).

Standard curves using pure acetaminophen in dissolution buffer (USP Reference Standard, Sigma-Aldrich) confirmed that all acetaminophen medications analyzed reached a dissolved drug concentration corresponding to full dissolution. Endpoint samples were within acceptable range of 500 mg acetaminophen in solution (data not shown).

## Data Analysis

Dissolution samples were company de-identified and data was processed and analyzed by a separate researcher.

Data was processed using MatLab with the Statistics and Machine Learning Toolbox and the Curve Fitting Toolbox (Release 2018a, The MathWorks, Inc). Dissolution profiles were normalized to the average of the last five data points and fit using a Weibull Model (cumulative distribution function for drug dissolved as a function of time equal to $f(t)=1-\exp[-a(t-T)^b]$, where $a$ and $b$ are parameters for time-scale and shape of curve progression, respectively, $t$ is time, and $T$ is lag time as a result of the dissolution process and was assumed to be zero). The fits were used to calculate times corresponding to percent of acetaminophen dissolved in solution. Time for 80% dissolution is reported following the USP monograph for acetaminophen dissolution at the time of this study, which specifies tolerance as greater or equal to 80% dissolution within 30 minutes [16].

## Results

The comparative efficacy of over-the-counter oral dosage acetaminophen products with marketing claims of rapid or fast-release was investigated using industry standard dissolution methods. Our comparative dissolution analysis revealed that rapid or fast-release gelatin coated acetaminophen tablets (gelcaps) from five major US companies dissolve on average 37 seconds slower than company-matched standard tablets (see Figure 1). 1,200 solid acetaminophen products for oral administration were analyzed throughout 30-minute intervals to provide strong statistical confidence in these results.

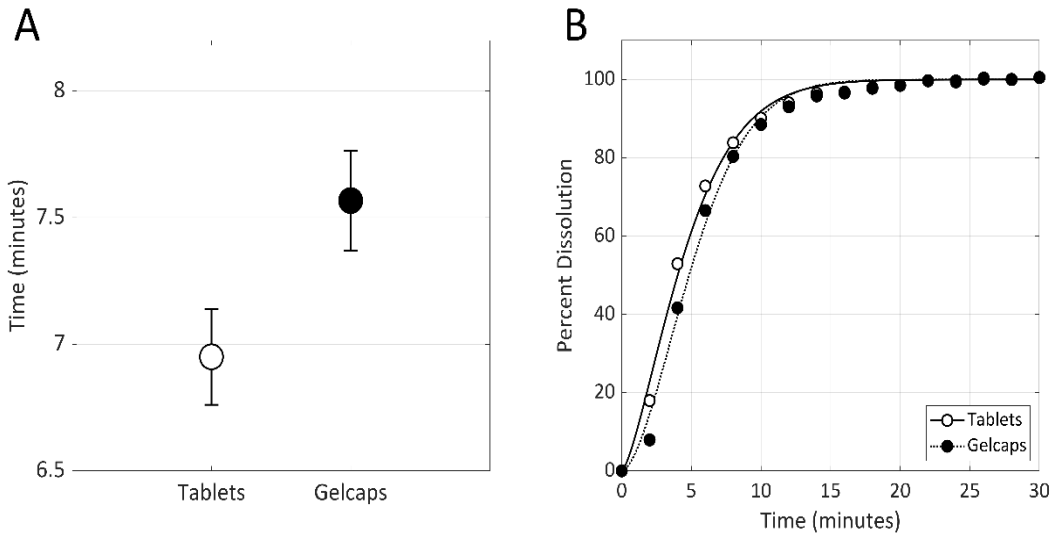


**Figure 1:** A) Time for 80% dissolution of over-the-counter acetaminophen comparing 600 standard tablets and 600 rapid or fast-release gelcaps across five companies reveals that rapid or fast-release gelcaps (black) take longer to dissolve compared to standard tablets (white). The p-value of 1.12E-05 suggests this time difference is strongly statistically significant. Error bars are 1.96 times standard error, indicating 95% confidence interval under the central limit theorem. B) Averaged and normalized UV absorption by acetaminophen in solution monitors percent dissolution as a function of time for all five companies.

Sampling every two minutes ensured a high accuracy in curve fitting using the Weibull model, which has been previously used to model the mechanics of dissolution for solid oral medications [17].

| | Tablet (minutes) | Gelcap (minutes) | % Difference | p-value |
|---|---|---|---|---|
| Avg Company #1 | 7.47 ± 0.10 | 9.18 ± 0.17 | +21.9% | 3.63E-17 |
| Avg Company #2 | 7.71 ± 0.10 | 8.73 ± 0.14 | +12.4% | 9.36E-09 |
| Avg Company #3 | 9.08 ± 0.19 | 7.56 ± 0.19 | -18.2% | 5.66E-08 |
| Avg Company #4 | 3.56 ± 0.05 | 3.94 ± 0.03 | +10.0% | 4.18E-09 |
| Avg Company #5 | 7.04 ± 0.25 | 8.43 ± 0.14 | +18.0% | 1.20E-08 |
| Medication Average | 6.95 ± 0.21 | 7.57 ± 0.20 | +8.5% | 1.12E-05 |

**Table 2:** Time for 80% dissolution comparing tablets (n = 120) and rapid or fast-release gelcaps (n = 120).

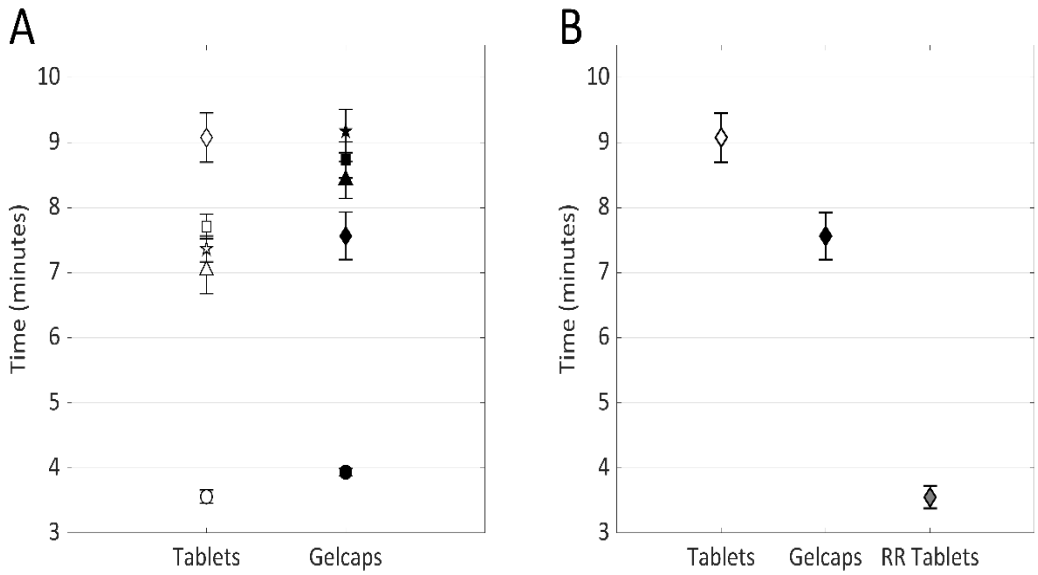


**Figure 2:** Time for 80% dissolution reveals significant company variability between companies and between medication type. A) Comparison of companies and tablet vs gelcaps: company #1 (stars), company #2 (squares), company #3 (diamonds), company #4 (circles), and company #5 (triangles). B) Company #3 comparison of time for 80% dissolution for tablets (n = 120, white), rapid or fast-release gelcaps (n = 120, black), and rapid-release tablets (n = 8, grey) shows that company #3 rapid or fast-release gelcaps are slower to dissolve compared to rapid-release tablets (p-value 1.79E-07).

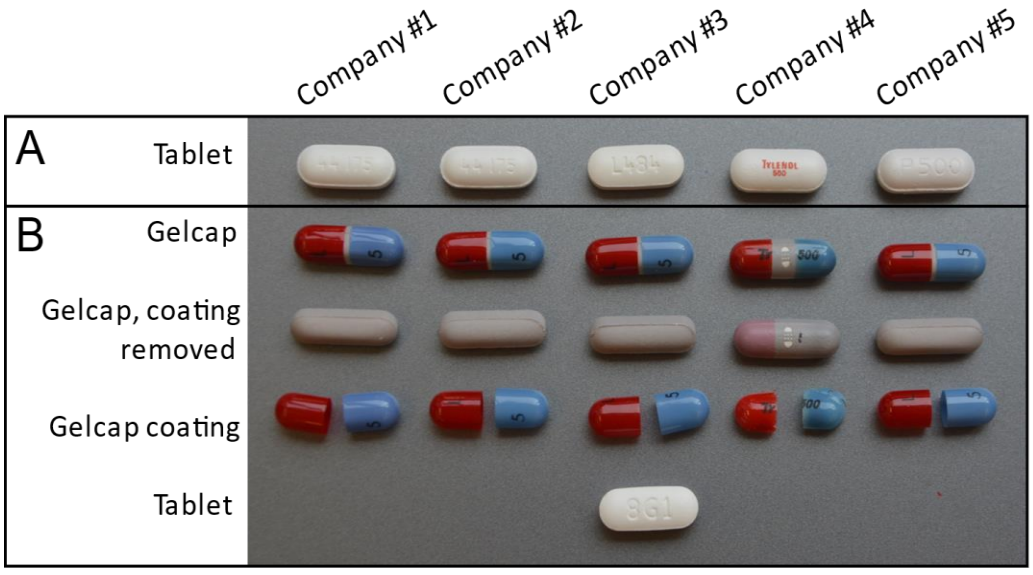


**Figure 3:** Examples of individual medications used in the study. A) Standard release products and B) rapid or fast-release products showing intact gelcaps and gelcaps with coating removed.

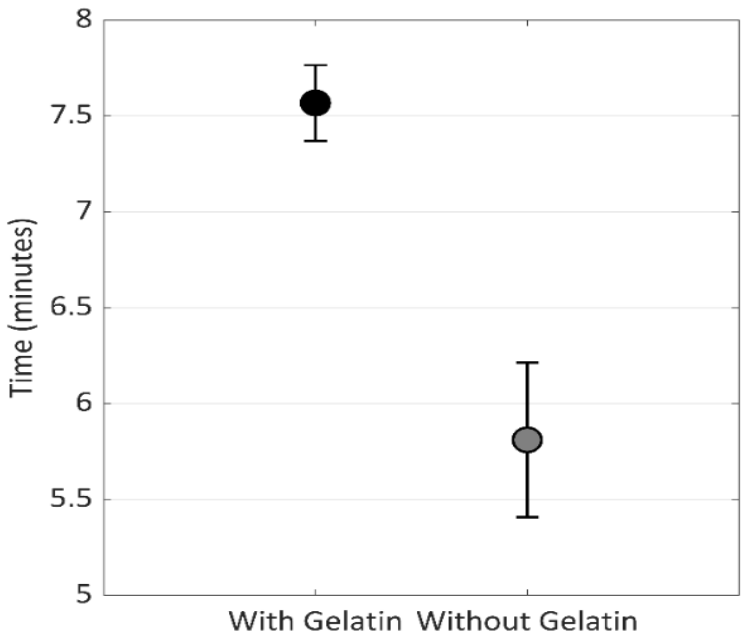


**Figure 4:** Removing the gelatin coating of rapid or fast-release gelcaps without gelatin, (n = 20), significantly decreases the time for acetaminophen to dissolve compared to rapid or fast-release gelcaps (with gelatin, n = 120). The p-value for the average time for dissolution of all companies between with coating and coating removed is 3.53E-11 underscoring a very strong statistical significance for these results.

| | Gelcap With Coating (minutes) | Gelcap, Coating Removed (minutes) | % Difference | p-value |
|---|---|---|---|---|
| Avg Company #1 | 9.18 ± 0.17 | 7.47 ± 0.32 | -20.6% | 1.39E-04 |
| Avg Company #2 | 8.73 ± 0.14 | 6.96 ± 0.24 | -22.7% | 2.20E-06 |
| Avg Company #3 | 7.56 ± 0.20 | 5.66 ± 0.32 | -28.8% | 1.05E-04 |
| Avg Company #4 | 3.94 ± 0.04 | 2.56 ± 0.07 | -42.6% | 5.67E-36 |
| Avg Company #5 | 8.43 ± 0.14 | 6.42 ± 0.25 | -27.1% | 2.35E-07 |
| Medication Average | 7.57 ± 0.20 | 5.81 ± 0.21 | -26.3% | 3.53E-11 |

**Table 3:** Time for 80% dissolution comparing gelcaps with (n = 120) and without (n = 20) gelatin coating. Average dissolution times for 20 gelaps from each company are shown.

For only one of the five companies (company #3), rapid or fast-release gelcaps dissolved faster than company-matched standard tablets. Company #3 standard tablets were, on average, the slowest dissolving medications. Notably, company #3 is, as far as we were able to reasonably determine in the New York Tri-State Area, the only company included in

this study that has also marketed an additional rapid or fast-release actetaminophen tablet that is not gelatin coated. Comparative analysis of this additional company #3 product from two different lots with company #3 gelcaps demonstrated that the gelcaps are statistically significantly slower than company-matched tablets (see Figure 2), preserving the trend that gelcaps dissolve slower than tablets.

To better understand the influence of gelatin coatings on gelcap dissolution, four gelcaps from each of the twenty-five lots tested during the primary study (n = 100) were examined with their red and blue encapsulation removed. All components were added to the dissolution vessel at the same time to ensure that the only variable changed was the physical attachment of the gelatin coating to the solid medication surface. Results suggest that the removal of a gelcap's red and blue coating speeds up, on average, the time required for fully dissolving by 26% (see Table 3). This faster dissolution time suggests that gelcaps are a barrier for dissolution (see Figure 4).

An unanticipated study result concerns variability between companies. Specifically, the variability of gelcaps and tablets between the five major US companies was surprisingly high. For example, at 80% dissolution and averaged over 120 gelcaps and 120 tablets, products sold by company #4 dissolve 2.4 (gelcaps) and 2.1 (tablets) times faster when compared with products sold by company #1 (see Figure 2A and Table 2).

## Discussion and Conclusions

Dissolution of orally administered solid therapeutic drugs is a critical step leading to the release of active drug and is rarely studied in detail. This study investigated over-the-counter oral medication with marketed claims of rapid or fast-release. These rapid or fast-release labeled medications are sold at an average of a 23% higher price [18], which make the claims associated with these medications of particular interest from a consumer perspective.

The results of the study suggest that acetaminophen gelcaps packaged with marketed claims of rapid or fast-release tend to dissolve slower than tablets of identical dosage sold by the same company.

All medications used for this study passed industry standards for full dissolution in under 30 minutes and are therefore predicted to be pharmacologically effective. Most drugs taken orally are absorbed in the small intestine due to high permeability and large surface area compared to the stomach [19]. As an early rate-limiting step, stomach emptying renders any oral medication that dissolves in 30 minutes or less essentially as rapid as possible in terms of dissolution. Indeed, unless oral medications are engineered for extended release, those that dissolve or disintegrate in the gastrointestinal tract are generally considered rapidly dissolving formulations. In these cases, bioavailability is dependent on drug permeability [20].

Acetaminophen is one of the most commonly used drugs in the world to treat acute and chronic pain [21]. In the US, acetaminophen currently costs between 0.01 and 0.43 USD per dose depending on quantity sold according to drugs.com market research [22]. Furthermore, a 2002 survey reported that 89% of consumers read over-the-counter drug package labels prior to purchase, which suggests that marketing claims like 'rapid release' or 'fast-release' may impact purchasing decisions [23]. Rapid or fast-release acetaminophen purchased for this study cost an average of 23% more than standard tablets of equivalent dose sold by the same company, suggesting there may be an economic impact for consumers choosing gelcaps over tablets.

Our results suggest that the gelatin coating added to rapid or fast-release gelcaps delays *in vitro* release of medication. We conclude that on average the gelcaps tested were approximately half a minute slower to dissolve compared to the company-matched tablets tested.

The results of this study warrant additional targeted investigations into acetaminophen products and, more generally, oral over-the-counter drugs marketed with release claims.

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## Disclaimer

Valisure LLC does not conduct drug development or participate in clinical trials. Valisure LLC's affiliated companies include a laboratory that tests pharmaceutical samples and a pharmacy that dispenses batch-tested pharmaceuticals.

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| Supplemental Information | | Lot 1 | Lot 2 | Lot 3 | Lot 4 | Lot 5 |
|---|---|---|---|---|---|---|
| **Standard Tablets** | Company #1 (Rite Aid) | P106590 | P105172 | P107562 | P104073 | P107150 |
| | Company #2 (Walgreens) | P103544 | P107562 | P106924 | P108010 | P107810 |
| | Company #3 (CVS) | 7HE1087 | 8BE1514B | 7ME1046 | 7LE1239A | 7ME1152 |
| | Company #4 (Tylenol) | LFA122 | LLC215 | LPC209 | LHA052 | LSA023 |
| | Company #5 (Equate) | C03724 | C08966 | C10960 | 7ME1482C | F00054 |
| **Rapid Release Gelcaps** | Company #1 (Rite Aid) | P106810 | P105884 | P107030 | P107550 | P107208 |
| | Company #2 (Walgreens) | P105691 | P107030 | P103593 | P107341 | P107676 |
| | Company #3 (CVS) | 71670091AB | P105483 | P106329 | P102607 | P108184 |
| | Company #4 (Tylenol) | LHA032 | LMA021 | LJA091 | LEA011 | MAA003 |
| | Company #5 (Equate) | P107790 | P108183 | P108696 | P108536 | P108038 |
| **Rapid Release Tablets** | Company #3 (CVS) | 7MR0309 | 7MR0310 | -- | -- | -- |

**Supplemental Table 4:** Lot numbers for medications used in the study.