



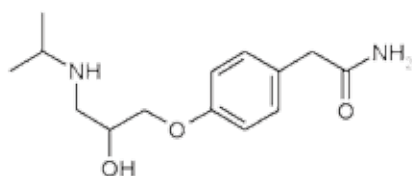
## Formulation and Stability Evaluation of Extemporaneously Prepared Atenolol Capsules from Crushed Atenolol Tablets

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### INTRODUCTION

In cardiology, beta blockers are an important class for the treatment of high blood pressure, arrhythmias, and angina pectoris, and for prevention of myocardial infarction. With long-term treatment, they reduce mortality and prolong survival in hypertensive patients and those with coronary heart disease. In neuropsychiatry, beta blockers have been used for the treatment of acute stress reactions and generalized anxiety, essential tremor, and prophylaxis of migraine.<sup>1</sup> Atenolol is chemically known as (RS)-2-{4-[2-hydroxy-3-(propan-2-ylamino) propoxy]phenyl} acetamide (Figure 1).

**FIGURE 1. Chemical structure of atenolol.**



Atenolol is one of the most widely used beta blockers in medicine. It is available for oral administration in some countries in 100-mg and 50-mg tablets, as is the case

### ABSTRACT

The purpose of this study was to formulate a 25-mg atenolol capsule starting from a commercial 100-mg atenolol tablet, given the fact that this strength is not available in Palestine and also because 50-mg atenolol tablets failed the splitting uniformity test of the *European Pharmacopoeia*, and to evaluate the chemical stability and dissolution behavior of the obtained capsules so as to ensure a high-quality product. A high-performance liquid chromatographic system was used for the analysis and quantification of atenolol in the samples studied. Samples of atenolol for analysis were prepared as reported by the *United States Pharmacopoeia* monograph. Disintegration and dissolution tests were performed according to the *United States Pharmacopoeia*. The high-performance liquid chromatography assay indicated that the 25-mg atenolol capsules were stable for four months when stored at ambient temperature conditions. The disintegration time for all atenolol capsules was within the *United States Pharmacopoeia* limits of 15 minutes. Atenolol release profile showed that approximately 90% of atenolol dissolved after 10 minutes. This study is important for patients who need to take one half of a 50-mg tablet, but for whom the splitting process doesn't give equal halves, and also for modifying the dose for patients with renal or hepatic problems. Therefore, it is possible for the community pharmacist to crush atenolol 100-mg tablets and refill them in new capsules with each containing a precise amount of atenolol, calculated according to body surface area and kidney and liver functions without affecting the chemical stability of the active ingredient nor its dissolution profile and also have a cost effective dosage form.

in Palestine. In a previous study conducted by Zaid et al, the 50-mg atenolol tablets produced by Jerusalem Pharmaceuticals Company failed the splitting test for both weight and content uniformity.<sup>2</sup> Tablet splitting is an important and widely spread practice in the field of pharmacy. Patients usually split tablets for various reasons, such as providing the patient with the desired dose when the product is not available in the required strength, starting therapy with the lowest possible doses

to reduce the incidence of side effects of certain drugs, reducing medication costs, and making the swallowing of large tablets easier.<sup>3-5</sup> Nevertheless, some problems may arise due to this practice, some of which may be patient related, while others may be attributed to the tablet or its formulation. The most important problem reported in this regard is the poor weight and content uniformity of the obtained halves.<sup>6-8</sup> Uneven splitting of a tablet may result in significant fluctuations of the

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administered dose. This may be clinically significant especially for drugs with a narrow therapeutic range.<sup>9</sup> The drug content of each unit should be within the acceptable limits around the label strength. Zaid et al suggested that when obtaining equal tablet halves is difficult, or when the desired dose is to be calculated according to the body surface area, or according to renal and liver functions, and this dose cannot be obtained even by splitting tablets into two equal halves, pharmacists can crush tablets and reformulate them into capsules in order to provide patients with equal drug doses.<sup>7</sup> However, concerns regarding the stability of the obtained capsules must be addressed and investigated. This study aims to evaluate the stability of extemporaneously prepared 25-mg capsules obtained from crushed 100-mg tablets and stored at 30°C and 65% RH.

## MATERIALS, INSTRUMENTS, AND METHODS

### Materials

Atenolol was purchased from IPCA Laboratories (India); Corotenol tablet (100-mg atenolol tablet) was donated from Jerusalem Pharmaceuticals Company (Ramallah-Palestine); colloidal silicon dioxide was obtained from Aerosil (Evonik, Germany); croscarmellose sodium was obtained from FMC Corporation (Ireland); magnesium stearate was obtained from Magnesia (Germany); microcrystalline cellulose was obtained from FMC Corporation (Avicel pH 101); polyethylene glycol was obtained from BASF (Germany); sodium lauryl sulphate was obtained from Cognis (Germany); talc was purchased from Beechamores (India); sodium hydroxide was obtained from Merck, KgaA (Darmstadt, Germany); and monobasic potassium phosphate was obtained from Merck, KgaA. The remaining chemicals used in this study were of analytical grade and obtained from commercial sources.

### Formulation of Atenolol Capsules

The 25-mg capsules containing atenolol were prepared starting with 50 atenolol 100-mg tablets of Corotenol. The tablets were crushed using a mortar and

pestle. The powdered tablets were passed through a No. 20 mesh. The resultant powder was diluted with microcrystalline cellulose (Avicel pH 101) to obtain a 1:1 mixture of powder. The mixture was filled into size 2 hard-gelatin capsules using a Manual Capsule Filling Machine (Zuma Srl, Milan Italy). The average final weight of the obtained capsule was 165 mg and each capsule contained 25 mg of atenolol. The capsules were filled in high-density polyethylene (HDPE) jars and sealed by a pressure-inductive sealing cap. Samples were taken for initial analysis, and the remaining samples were stored at 30°C and 65% RH to be analyzed at 1, 2, and 4 months.

### Instruments

A high-performance liquid chromatographic (HPLC) system from Merck Hitachi (Interface module D-7000, Autosampler L-7200, Pump L-7100, Detector L-7450) was used for the analysis and quantification of atenolol in the samples studied. Separation was accomplished using a 300 mm x 3.9 mm L1 Octadecylsilane C18 column chemically bonded to totally porous silica par-

ticles, 5.0 mcm in diameter. An electronic balance (Precisa 205 ASCS) was used for weight measurements.

## QUALITY CONTROL OF ATENOLOL CAPSULES

### Weight Uniformity Test

To assess the weight uniformity, the gross weight of each capsule was measured. The contents of each capsule were removed, and the emptied shells were accurately weighed individually. The net weight of each capsule's content was calculated by subtracting the weight of the shell from the respective gross weight. The percentage deviation of the individual capsules from the mean was determined according to compendial requirements of the *USP*.<sup>10</sup>

### Assay of Atenolol in the Capsules

The amount of atenolol in the whole capsule was determined according to the *USP* assay method.<sup>10</sup> The HPLC system was used for the analysis and quantification of atenolol in the studied samples. Separation was accomplished using a 300 mm x 3.9 mm, 5.0 mcm RP-C18 column (Table 1).

### Preparation of Samples for Analysis

Samples of atenolol for analysis were prepared as reported by the *USP* monograph for the analysis of atenolol tablets. The contents of each capsule were placed in a 100-mL volumetric flask, adding 10 mL of dimethylsulfoxide, and adjusting to volume with deionized water. Samples were diluted with deionized water in 5-mL volumetric flasks in order to obtain a concentration close to the middle of the linear range of the

**TABLE 1. Summary of High-performance Liquid Chromatographic Parameters for Atenolol Assay.**

PARAMETER	SPECIFICATION
Column	300 mm x 3.9 mm, 5.0 mcm RP-C18
Flow rate	0.6 mL/minute
Injection volume	10 µL
Wavelength	226 nm
Mobile phase	pH 3.0 ± 0.1 phosphate buffer:methanol (7:3)

**TABLE 2. Evaluation Results of Atenolol Capsules (Stored at 30°C and 65% RH) Over a Period of Four Months.**

TIME (MONTHS)	STORAGE CONDITIONS 30°C			PERCENTAGE OF DISSOLVED DRUGS AFTER 30 MINUTES
	AVERAGE WEIGHT	PERCENTAGE OF DRUG CONTENT	DISINTEGRATION TIME (MINUTES)	
0	170.2 ± 5.3	100.2	6 ± 1	99 ± 5
2	171.2 ± 7.2	103	7 ± 2	100 ± 4
4	167.5 ± 6.2	100.8	8 ± 1	98 ± 5

calibration graph. Duplicate five injections were made.

### Stability Study

All prepared capsules were filled in opaque plastic and well-sealed bottles. Bottles containing the capsules were stored at  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $65\% \pm 5\%$  RH. The 25-mg atenolol capsules were analyzed in duplicate by HPLC over the period of 0, 2, and 4 months. The results are shown in Table 2. All atenolol concentrations were expressed as percentages of initial concentration. Stability was defined as a concentration in the range of 90% to 110% of the initial value and dissolution not less than 80% (Q) of the labeled amount of atenolol ( $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_3$ ) within 30 minutes.

### Disintegration Test

The disintegration time of atenolol capsules was determined according to the procedure reported in the *USP*.<sup>10</sup> In summary, one capsule was placed in each of the six tubes of the basket and the disintegration apparatus operated using water as the disintegration media and maintained at  $37^{\circ}\text{C}$ . At the end of the time limit specified in the *USP* monograph, all of the capsules should be completely disintegrated.

### Dissolution of Atenolol Capsules

*In-vitro* dissolution studies were carried out using a dissolution apparatus *USP* (Type II) at a paddle speed of 50 rpm. Twelve capsules were selected for the dis-

solution study. The dissolution medium was 900 mL of pH 4.6 acetate buffer, and it was maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . In all dissolution experiments, 5 mL of dissolution samples were withdrawn and replaced with equal volume fresh acetate buffer (pH 4.6) at regular intervals. The samples were filtered through a Millipore filter 0.45  $\mu\text{m}$ . The amount of atenolol in the samples was determined using the above HPLC method.<sup>10</sup> The dissolution profile of atenolol capsules was generated from the graph of the percent of atenolol released versus time using Microsoft Office Excel. In fact, samples were periodically collected and tested at 0, 5, 10, 15, and 30 minutes, and the amount of atenolol in each sample was plotted against time as shown in Figure 2.

### Results

Visual inspection of the prepared capsules showed no signs of defect in all tested capsules stored at  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $65\% \pm 5\%$  RH. The tested capsules complied with *USP* requirements of weight uniformity and had an average weight of 165.0 mg/capsule. Stability was defined as a concentration in the range of 90% to 110% of the initial value. The initial concentration of the drug was designated as 100%. All subsequent concentrations were expressed as percentage of initial concentration, and they were close to 100%, showing high conformity with the *USP* requirement, as reported in Table 2. There were no detectable degradation

products at any time of the period of analysis. The disintegration time for all atenolol capsules was within the *USP* 15-minute limits, as reported in Table 2. Also, the percentage of atenolol release from capsules after 30 minutes was within the accepted *USP* limits for immediate-release oral dosage forms, and

it was higher than 98% at the end of the study period of four months. Moreover, the atenolol release profile showed that about 90% of atenolol was dissolved after 10 minutes, as reported in Figure 2.

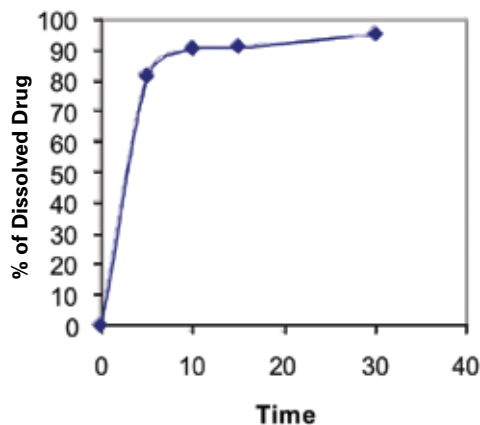
## DISCUSSION

The weight and content uniformity tests are among the most important quality-control *USP* tests with which tablets should comply in order to be commercialized. Unfortunately, sometimes the desired dose strength is not available on the market. In this case, patients may split tablets into two halves if the desired dose is 50% of an existing scored tablet. This practice, however, may not be useful when the desired dose must be calculated according to certain pharmacokinetic parameters. This is especially true for elderly patients who suffer from kidney or liver problems, and the calculated dose is less than 50% of the dose of an existing tablet. For those patients who practice tablet splitting, one would hope that the quality of the medication is maintained after the tablet has been split, including accurate medication dosage and desired therapeutic effect.

Many studies have been conducted to explore the weight uniformity of obtained halves, but, unfortunately, most of the studies demonstrated that obtaining equal halves is a difficult issue, and, therefore, many patients may take erratic doses when they follow this practice.<sup>6-8, 11-12</sup> Accordingly, there have been several studies which suggested solutions for this problem such as:

- Using tablet splitters (These devices do not really improve the accuracy of breaking.<sup>13-14</sup>)
- Asking the pharmaceutical manufacturers to manufacture scored tablets that split easily and equally<sup>8, 14-15</sup> or to produce tablets with different strengths in order to satisfy the pharmaceutical need for finding the appropriate dose strength<sup>7</sup>
- Assessing patients for their ability to understand and comply with regimens involving split tablets<sup>16</sup>
- Asking the pharmacist to divide the tablets for the patient and weigh the obtained halves, then

**FIGURE 2. Dissolution profile of 25-mg atenolol capsules.**



discard the failed ones or, alternatively, ask the pharmacist to crush the tablets and fill the content into new capsules with the desired strength<sup>7</sup>

Atenolol oral dosage forms are available in Palestine in two strengths (100-mg and 50-mg tablets). However, other strengths may be prescribed by physicians in order to adjust the dose for patients with renal or hepatic problems. Accordingly, many patients try to divide the 50-mg tablets in order to obtain 25-mg doses of atenolol. Unfortunately, an earlier study that was conducted on a local Palestinian product of 50-mg atenolol tablets showed that this product failed the *European Pharmacopoeia (EP)* splitting test.<sup>2,8</sup> The extemporaneous compounding of atenolol capsules with the desired strength by crushing the existing commercial atenolol tablets would be a valid alternative to achieve the desired strength if the obtained capsules can pass the *USP* and/or *EP* weight, uniformity, stability, disintegration time, and dissolution profile requirements for immediate-release oral solid dosage forms. Furthermore, it was found to be a cost-effective alternative, as four capsules could be obtained out of each 100-mg tablet. Accordingly, the first purpose of this study was to prepare atenolol 25-mg capsules starting from a commercially available product of atenolol tablets. The second purpose of this study was to evaluate properties of the obtained capsules with regard to weight uniformity, chemical stability, disintegration time, and dissolution behavior according to the *USP* monograph of atenolol so as to ensure high quality of the obtained capsules.

Atenolol 25-mg capsules being used as an antihypertensive, antianginal, and antiarrhythmic agent should be formulated in a manner to produce its desired therapeutic effects within a suitable time period. From an economic point of view, it was decided in this study to use 100-mg atenolol tablets to be crushed instead of 50-mg atenolol tablets, since both products were equal in price, thus, it was more cost effective to use 100-mg tablets, as each one should give four capsules. In this manner, we have avoided uneven tablet halves resulting from splitting of 50-mg tablets. In fact, the practice of tablet splitting is frequently

pursued in the field of pharmacy, especially when patients need lower doses of products, which are not available commercially, and especially in patients with renal or hepatic problems, or when a reduction of the cost of therapy is required.<sup>3-5</sup>

The results of this study have shown that the compounded atenolol capsules were stable along the period and conditions of the stability study, since they passed the chemical and other *USP* tests for immediate-release solid dosage forms. In fact, the obtained capsules were stable for at least four months when stored at  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $65\% \pm 5\%$  RH. The capsules showed a disintegration time that was within the limits prescribed by the *USP* so as not to compromise the dissolution of atenolol in the stomach, which is an essential step to achieve immediate drug absorption. The dissolution test was carried out since the dissolution of drug from oral solid dosage forms is a necessary criterion for drug bioavailability. In fact, dissolution studies can give an idea about the amount of drug available for absorption after oral administration. The release of atenolol from capsules was about 90% after 10 minutes, which indicates that an appropriate amount of atenolol was available for absorption.

A study conducted by Vogelpoel et al<sup>17</sup> suggested that atenolol immediate-release tablets may be bioequivalent from bioequivalence study if the release of atenolol from the dosage form is higher than 85% in 15 minutes. Accordingly, the release behavior shown in this study encourages the preparation of atenolol capsules by crushing the tablets, which will not affect the stability of the product nor its therapeutic response since it releases most of its content within 10 minutes. This type of study may be extended to many other scored tablets which may not give equal halves when they are divided. Pharmaceutical manufacturers should always attempt to produce tablets that split equally or at least provide their package inserts with scientific information and directions on how to transform their commercial tablets into capsules as well as information on the expiration date of the obtained capsules. In fact, this may result in higher dose accuracy and may also promote the marketing of such tablets since pharmacists should use only tablets accompanied by this type of information in their package insert.

The limitations of this study is that it includes only one product (atenolol 25 mg), which may be available in many countries, making it unnecessary to split the 50-mg tablets. However, the idea of this study may be extended to many other scored tablets which may not give equal halves when they are divided.

## CONCLUSION

The HPLC assay indicated that the 25-mg atenolol capsules were stable for four months when stored at  $30^{\circ}\text{C}$  and 65% RH. The dissolution profile of these capsules indicates immediate and high release of atenolol, which is an essential condition to ensure the required absorption. This study is of great importance for patients who need to take tablet halves and the splitting process is not giving equal halves. Pharmacists can prepare good-quality capsules with the desired atenolol content using Corotenol (100-mg atenolol tablet) as a source of active ingredient. In those cases, pharmaceutical manufacturers should provide their package inserts with scientific information and directions on how to transform their commercial immediate-release tablets into capsules, as well as provide information on the expiration date of the obtained capsules.

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