

## Divisibility of Bisoprolol and Amlodipine Fixed-dose Combination Tablets

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### Abstract

**Background:** Bisoprolol/amlodipine fixed-dose combination (FDC) tablets for the treatment of hypertension have been designed with a score line to facilitate breaking for ease of swallowing.

**Objective:** To evaluate if splitting bisoprolol/amlodipine FDC tablets by hand is a viable strategy to obtain lower doses of the FDC than those currently available.

**Methods:** The degree of weight and content variation between bisoprolol/amlodipine (5 mg/5 mg, 5 mg/10 mg) FDC tablet halves was assessed according to the European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP). Weight uniformity was assessed by comparing the weight of tablet halves with their respective whole-tablet weight divided by two, and by comparing individual weights with the average weight of tablet halves from each respective batch. Content uniformity was assessed by determining the amount of each drug in tablet halves, expressed as a percentage of half the labeled dose, and the quantity of each drug released from tablet halves in a dissolution test.

**Results:** The weights of all tablet halves tested were within the limits of the average weight defined by the Ph. Eur. (85% - 115%) and the USP (75% - 125%). The dose content of each drug in all tablet halves tested were within the defined limit for variability ( $\leq 15\%$ ) and the average quantities of active drug released were above the limits for both bisoprolol (85%) and amlodipine (80%).

**Conclusion:** Both tablets met the Ph. Eur. and USP criteria for weight and content uniformity, suggesting that bisoprolol/amlodipine FDC tablets can be split by hand for dose adjustment.

**Keywords:** Bisoprolol; Amlodipine; Fixed-Dose Combination; Hypertension; Blood Pressure Control; Tablet Splitting

### Abbreviations

BB: Beta-Blockers; CCB: Calcium Channel Blockers; ESC: European Society of Cardiology; ESH: European Society of Hypertension; FDC: Fixed-Dose Combination; Ph. Eur.: European Pharmacopeia; USP: United States Pharmacopeia; HPLC-UV: High-Performance Liquid Chromatography Coupled with Ultraviolet Detection; MAH: Market Authorization Holder; AV: Acceptance Value

### Introduction

Hypertension is one of the most prevalent health problems worldwide; it was estimated to affect more than 1 billion adults in 2015 [1] and this number is expected to rise further over the next decade [2]. Hypertension is a major risk factor for cardiovascular diseases such as myocardial infarction, stroke, and heart failure [3] and it is responsible for approximately half of the 17 million deaths due to cardiovascular disease that occur every year [4].

Control of blood pressure is key for decreasing the risk of morbidity and mortality due to cardiovascular disease [5]. The following five main classes of blood pressure lowering agents are currently recommended for the treatment of hypertension: beta-blockers (BB), calcium channel blockers (CCB), diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [6,7]. Evidence suggests that most patients require a combination of drugs targeting different pathways to achieve blood pressure targets [8]. Combining drugs may have additive effects and result in significantly greater reductions in blood pressure than if increasing the dose of one drug alone [9]. Indeed, the most recent guidelines from the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [7] and the Chinese Guidelines for Prevention and Treatment of Hypertension [6] recommend initiating antihypertensive therapy using a combination of two drugs from the five main classes of blood pressure lowering agents.

Bisoprolol (a BB) and amlodipine (a CCB) are frequently used as monotherapies for the treatment of hypertension, and their complementary modes of action [8] make them suitable for use as a combination therapy. Current ESC/ESH treatment guidelines recommend using a BB/CCB combination as initial therapy in hypertensive patients with coronary artery disease or atrial fibrillation [7]. BB/CCB is also one of the combinations for initial antihypertensive therapy that is recommended in the Chinese treatment guidelines [6]. Single-pill combination treatment is the preferred strategy to manage hypertension [6,7] as it reduces treatment complexity by reducing the number of pills required, which improves patient adherence to treatment regimens [10]. A fixed-dose combination (FDC) of bisoprolol and amlodipine was therefore developed for ease of administration and to improve patient adherence rates. The bisoprolol/amlodipine FDC has been shown to be effective in treating hypertension when adequate blood pressure control has not been achieved with either amlodipine or bisoprolol as monotherapy alone [11] and as a substitution therapy for the free-dose combination [12,13].

Bisoprolol/amlodipine FDC tablets are available in several dose strengths (5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg), providing flexibility in terms of dosing and the ability to increase the dose of one drug independently of the other. This allows the antihypertensive therapy to be tailored to the patient. However, some physicians, for example in China, prefer to prescribe lower doses of bisoprolol than those currently available in an FDC with amlodipine (oral communication). Because bisoprolol/amlodipine FDC tablets have been designed with a score line intended to facilitate breaking for ease of swallowing, further dosing flexibility could be achieved through tablet division, which has become common practice in health care as a means of adjusting the dose [14,15]. Criteria for tablet divisibility have been introduced by the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopoeia (USP) to ensure that the weight and content uniformity between split tablet portions are within a narrow range and deliver accurate therapeutic doses. The aim of this study was to investigate the degree of weight and content uniformity between split tablet halves of bisoprolol/amlodipine (5 mg/5 mg, 5 mg/10 mg) FDC tablets according to the Ph. Eur. and the USP criteria, and evaluate whether splitting tablets is a viable strategy to provide lower doses of the FDC. Tablets with the lowest dose of bisoprolol (5 mg) were used in this study to address the preference of some physicians to prescribe lower doses of this drug. Tests for uniformity of mass, uniformity of dosage units, and dissolution from both the Ph. Eur. and USP were chosen to assess the divisibility of bisoprolol/amlodipine FDC tablets.

## Materials and Methods

### Materials

Bisoprolol fumarate/amlodipine besylate (5 mg/5 mg, 5 mg/10 mg) FDC tablets (Concor AM; Merck KGaA, Darmstadt, Germany) were used for uniformity of mass, uniformity of dosage units, and dissolution tests. Three batches for each dose were tested, referred to as batches 1 - 3 for the 5 mg/5 mg dose and 4-6 for the 5 mg/10 mg dose.

### Test for uniformity of mass

The uniformity of mass was assessed according to both the Ph. Eur. [16] and the USP [17] criteria, using the same tablet halves in both tests. In the test described by the USP [17], a random sample of intact tablets ( $n = 30$ ) was taken from each batch, and each tablet was weighed. Tablets were split by hand without mechanical assistance along the score line, and the split halves of each tablet were weighed. The expected weights of tablet halves were calculated by dividing the weight of the respective whole tablet by two. Acceptance criteria

were met if the tablets split into two halves, and the weight of each split half was within 75%-125% of its expected weight for at least 28 of the 30 tablets.

In the Ph. Eur. test [16], one tablet half from each of the 30 split tablets from the USP test were weighed, and the average weight for the 30 portions was calculated. Acceptance criteria were met if the mass of  $\leq 1$  portion was outside the limits of 85% - 115% of the average mass, and if all the split halves were within the limits 75% - 125% of the average mass.

### Test for uniformity of dosage units

Tests of the uniformity of dosage units were performed according to the Ph. Eur. [18] and the USP [19] using tablet halves that met the uniformity of mass criteria. The amount of bisoprolol and amlodipine in tablet halves was measured at Alphalytik Pharmaservice GmbH, Berlin, using high-performance liquid chromatography coupled with ultraviolet detection (HPLC-UV) according to the official quality control testing procedure of the market authorization holder (MAH). The test was performed using 20 tablet halves (10 right and 10 left) from each batch. The average ( $\bar{x}$ ) amount of both bisoprolol and amlodipine in tablet halves from each batch, expressed as a percentage of half the labeled dose, was calculated. The acceptance value (AV) for each portion of tablet halves was calculated according to the following equation:

$$|M - \bar{x}| + ks,$$

where M is a reference value ( $M = \bar{x}$  if  $98.5\% \leq \bar{x} \leq 101.5\%$ ,  $M = 98.5\%$  if  $\bar{x} < 98.5\%$ ,  $M = 101.5\%$  if  $\bar{x} > 101.5\%$ ), k is the acceptability constant ( $k = 2.4$  if  $n = 10$ ,  $k = 2.0$  if  $n = 30$ ) and s is the sample standard deviation. Acceptance criteria were met if the AV of the portions of right and left tablet halves were both  $\leq 15.0\%$ . If an AV was 15.0%, a further 40 halves (20 right and 20 left) that complied with the uniformity of mass criteria from the respective batch were tested, and the AV was recalculated for the final sample (60 halves; 30 right and 30 left). Acceptance criteria were met if the final AV was  $\leq 15.0\%$  and no individual split half had a content lower than 0.75M or higher than 1.25M.

### Dissolution test

Split tablet halves ( $n = 12$ ) from each batch that complied with the criteria for uniformity of mass were used for the dissolution test. Dissolution testing was performed at Alphalytik Pharmaservice GmbH, Berlin, with a paddle apparatus (Ph. Eur./USP apparatus 2) and subsequent HPLC-UV methodology according to the official quality control testing procedure of the MAH. Acceptance criteria were met if the average dissolved active substance (Q) for the 12 tablets halves was  $\geq 85\%$  for bisoprolol and  $\geq 80\%$  for amlodipine after 30 minutes and no individual value was  $< 70\%$  for bisoprolol and  $< 65\%$  for amlodipine (Merck KGaA, data on file).

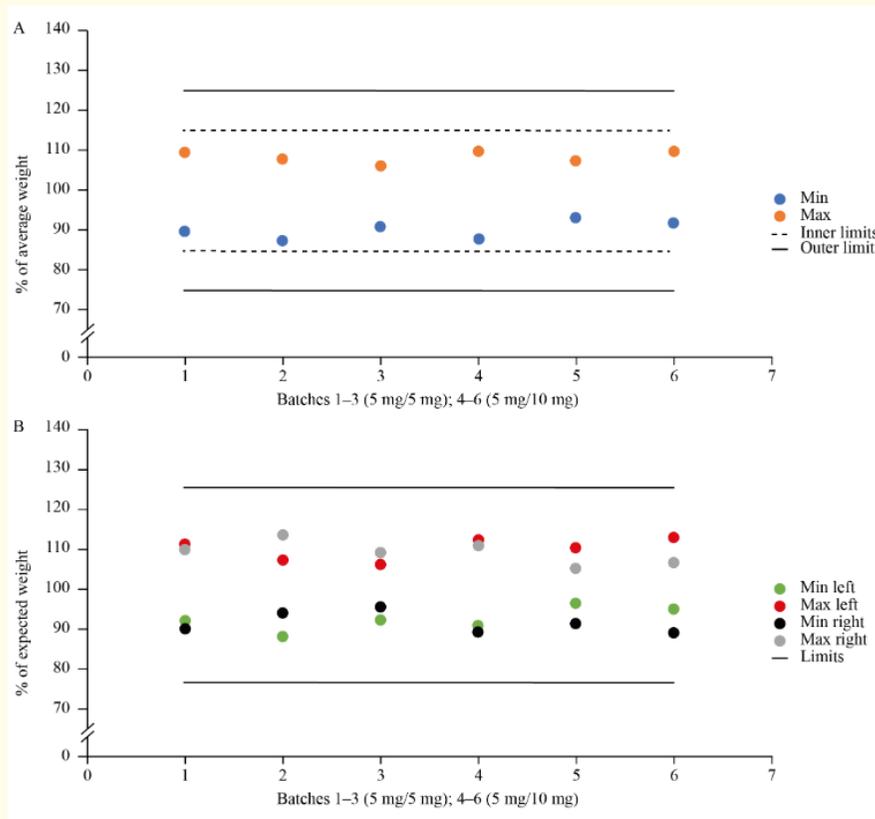
## Results

### Uniformity of mass

Criteria for uniformity of mass outlined by both the Ph. Eur. and USP were met for tablets from all batches. In the uniformity of mass test according to the Ph. Eur., no individual split half was outside the outer (75% - 125%) or the inner (85% - 115%) limits of the average mass for each batch (Figure 1A). In the USP test, the weights of split tablet halves from all batches were within the limits 75%-125% of the expected weights (Figure 1B).

### Uniformity of dosage units

Criteria for uniformity of dosage units were met for tablet halves from all batches tested. The AV for some tablet halves was close to or above the limit of 15.0% ( $n = 10$ ), the latter requiring further tablet halves to be tested and final AV to be recalculated ( $n = 30$ ). However, the final AV for all portions was below the limit in all cases (Table 1).



**Figure 1:** The uniformity of mass between tablet halves according to the Ph. Eur. (A) and the USP (B). Acceptance criteria:  $\leq 1$  tablet half outside the limits of 85 - 115% of the average mass, and all 30 tablet halves within the limits 75%-125% (Ph. Eur.); and within the limits of 75% - 125% of the expected weights for  $\geq 28$  of the 30 tablets (USP).

Tablet (mg biso/amlo)	Batch	Acceptance value (%)			
		Left biso	Left amlo	Right biso	Right amlo
5/5	1	14.0	11.1	14.2	12.4
	2	10.8*	12.7*	11.2*	11.4*
	3	6.3	10.3	8.4	6.1
5/10	4	11.0*	11.1*	11.6*	12.6*
	5	13.2*	9.3*	10.2	10.4
	6	11.7	10.8	10.8	10.7

**Table 1:** Acceptance values for content uniformity between tablet halves according to the Ph. Eur. and USP.

Asterisk denotes where  $n = 30$  tablet halves were used;  $n = 10$  for all other portions.

Acceptance criteria: acceptance value  $\leq 15.0\%$ .

Aml: Amlodipine; biso: Bisoprolol.

## Dissolution

Tablets from all batches passed the dissolution test. The average quantity of bisoprolol or amlodipine released in 30 minutes for all batches tested was above the limits of 85% and 80% for bisoprolol and amlodipine, respectively. The minimum amount of drug released from any individual tablet half was not below the minimum limits of 70% for bisoprolol and 65% for amlodipine (Table 2).

Tablet (mg biso/ amlo)	Batch	Prescribed dose released (%)			
		Biso		Amlo	
		Average	Minimum	Average	Minimum
5/5	1	99.4	95.1	99.4	95.1
	2	98.4	89.6	97.1	82.4
	3	96.4	86.8	95.9	86.6
5/10	4	101.3	86.1	101.5	85.4
	5	101.6	90.9	101.9	90.2
	6	100.6	93.1	100.6	92.7

**Table 2:** Percentage of prescribed dose of bisoprolol and amlodipine released in dissolution tests on tablet halves ( $n = 12$ ).  
Acceptance criteria: prescribed dose release  $\geq 85\%$  for biso and  $\geq 80\%$  for amlo after 30 minutes, and no individual value  $< 70\%$  for biso and  $< 65\%$  for amlo. Amlo, amlodipine; biso, bisoprolol.

## Discussion

Bisoprolol/amlodipine (5 mg/5 mg, 5 mg/10 mg) FDC tablets, split by hand along the score line, were tested to assess the uniformity of mass and dosage units between tablet halves according to the Ph. Eur. and the USP. The weight and drug content of all tablet halves tested were within the limits defined by both pharmacopeias.

Recent clinical guidelines for the management of hypertension recommend using a combination of two or more drugs with different modes of action, preferably as an FDC in a single pill [6,7]. Using a combination of drugs has the advantage of better efficacy due to additive drug interactions [9]. Using an FDC reduces the number of required pills compared to administering the same drugs separately, which improves patient adherence to treatment regimens [10]. Bisoprolol/amlodipine FDC tablets are available in various dose strengths (5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg), providing the additional advantage of dose flexibility.

The preference of some physicians to prescribe lower doses of bisoprolol than currently available in an FDC with amlodipine suggests that further dosing options may be useful in a clinical setting. One method to provide lower doses is to split tablets into smaller portions, which has become common practice in health care as a means for increasing dose flexibility where desired doses are not available and/or reducing the cost of therapy [14,15].

There are risks associated with the division of tablets, including tablets splitting into uneven parts or losing mass upon splitting [15], which may result in patients receiving incorrect drug doses. The accuracy of tablet division varies according to a tablet's physical properties [15]. Tests for the accuracy of tablet division have been introduced by national and international pharmacopeias to ensure consistency of mass and dosage units between split tablet portions so that patients receive the intended dose. These tests are also recommended by regulatory bodies; for example, the Center for Drug Evaluation and Research of the Food and Drug Administration has described the tests required to assess the accuracy of splitting of scored tablets in a recent guideline [20].

## Conclusion

Bisoprolol/amlodipine FDC tablets were designed with a score line intended to facilitate breaking for ease of swallowing. The results of this study demonstrate that bisoprolol/amlodipine 5 mg/5 mg and 5 mg/10 mg FDC tablets, split by hand along this score line, meet acceptance criteria on mass and dosage unit uniformity defined by the Ph. Eur. and USP. The accuracy and uniformity of the weight and drug content between split tablet halves of bisoprolol/amlodipine FDC tablets suggests that splitting these tablets by hand is a viable strategy to obtain lower doses of the FDC than those currently available. This may provide physicians with further dosing flexibility with the bisoprolol/amlodipine FDC for the management of hypertension.

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## Conflicts of Interest

Phillip Krüger and Ulrike Gottwald-Hostalek are employees of Merck KGaA. Ningling Sun has no conflicts of interest to declare.

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