

## ベニジピン塩酸塩錠 4mg 「タイヨー」の溶出試験

### 緒言

ベニジピン塩酸塩錠 4mg 「タイヨー」につき、先発の標準製剤を対照として、下記に示す後発医薬品の生物学的同等性試験のガイドラインに従い、溶出試験を実施した。

### 試験方法

#### (1) 製剤

標準製剤：協和発酵工業(株)製 コニール錠 4 (ロット 792ACF)

試験製剤：大洋薬品工業(株)製 ベニジピン塩酸塩錠 4mg 「タイヨー」(ロット K7XK)

#### (2) 試験条件

試験法：溶出試験法第2法(パドル法)

試験液温：37

試験液量：900mL

試験液：日局第1液(pH1.2)，McIlvaineの緩衝液(pH5.0)，日局第2液(pH6.8)，  
水(日局精製水) <回転数：毎分50回転>

：日局第2液(pH1.2) <回転数：毎分100回転>

ベッセル数：各12ベッセル

測定方法：液体クロマトグラフ法

### 試験結果

標準製剤を対照としたベニジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果を表1~5及び図1~5にそれぞれ示す。

表1 ベニジピン塩酸塩錠 4mg「タイヨー」の溶出試験結果 (pH1.2, 50rpm)

| 製剤   | ベッセル数 | 時間 (分) |      |      |       |       |       |
|------|-------|--------|------|------|-------|-------|-------|
|      |       | 5      | 10   | 15   | 30    | 45    | 60    |
| 試験製剤 | 1     | 12.8   | 40.7 | 65.2 | 95.6  | 102.0 | 103.5 |
|      | 2     | 17.0   | 48.4 | 73.4 | 98.1  | 105.4 | 106.4 |
|      | 3     | 27.8   | 63.3 | 84.6 | 101.3 | 101.8 | 103.3 |
|      | 4     | 27.9   | 66.8 | 90.0 | 100.0 | 101.5 | 102.5 |
|      | 5     | 11.6   | 37.3 | 60.3 | 92.3  | 101.4 | 103.3 |
|      | 6     | 14.3   | 48.3 | 73.6 | 103.4 | 104.9 | 106.5 |
|      | 7     | 8.3    | 34.8 | 57.2 | 88.8  | 96.1  | 102.5 |
|      | 8     | 14.4   | 43.3 | 63.2 | 98.2  | 101.2 | 102.0 |
|      | 9     | 20.5   | 56.5 | 81.0 | 103.4 | 103.2 | 104.4 |
|      | 10    | 2.6    | 56.0 | 82.9 | 102.8 | 103.2 | 104.8 |
|      | 11    | 26.1   | 66.0 | 88.4 | 100.4 | 101.6 | 102.5 |
|      | 12    | 6.9    | 34.3 | 41.6 | 95.8  | 101.6 | 102.8 |
|      |       | 平均     | 15.9 | 49.6 | 71.8  | 98.3  | 102.0 |
|      | 標準偏差  | 8.3    | 11.9 | 14.6 | 4.6   | 2.3   | 1.5   |
| 標準製剤 | 1     | 41.3   | 57.2 | 71.7 | 97.0  | 98.8  | 96.7  |
|      | 2     | 37.9   | 74.9 | 87.5 | 93.4  | 88.2  | 87.9  |
|      | 3     | 29.8   | 59.2 | 94.5 | 92.3  | 98.5  | 84.4  |
|      | 4     | 13.0   | 35.0 | 61.4 | 87.0  | 91.2  | 81.0  |
|      | 5     | 14.1   | 38.9 | 54.3 | 89.1  | 84.5  | 92.5  |
|      | 6     | 22.1   | 51.8 | 83.6 | 94.3  | 84.0  | 88.8  |
|      | 7     | 24.0   | 60.6 | 84.5 | 100.9 | 100.6 | 93.3  |
|      | 8     | 47.2   | 86.9 | 98.1 | 100.1 | 97.7  | 100.4 |
|      | 9     | 26.1   | 63.2 | 86.7 | 97.5  | 95.2  | 96.2  |
|      | 10    | 24.6   | 58.6 | 89.5 | 99.2  | 98.6  | 99.4  |
|      | 11    | 38.4   | 85.8 | 95.9 | 100.0 | 94.8  | 94.2  |
|      | 12    | 28.5   | 70.5 | 94.5 | 100.7 | 102.7 | 102.3 |
|      |       | 平均     | 28.9 | 61.9 | 83.5  | 96.0  | 94.6  |
|      | 標準偏差  | 10.6   | 16.1 | 14.0 | 4.7   | 6.2   | 6.5   |

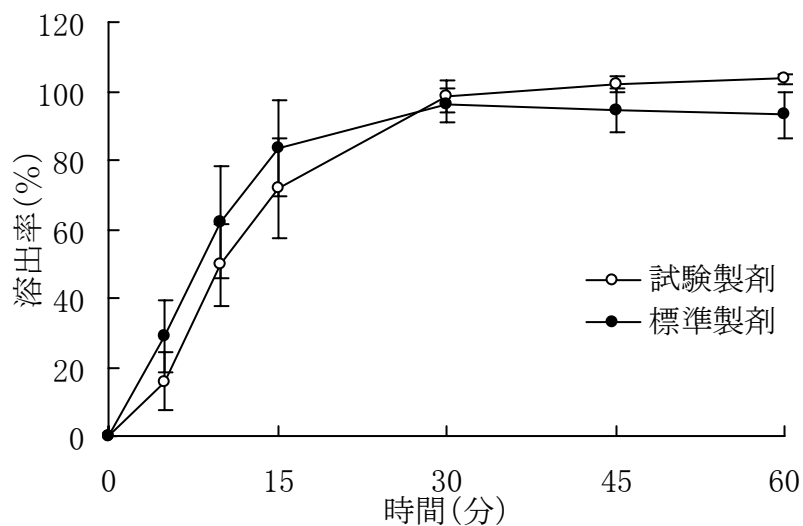


図1 ベニジピン塩酸塩錠 4mg「タイヨー」の溶出試験結果 (pH1.2, 50rpm)

表2 ベニジピン塩酸塩錠 4mg「タイヨー」の溶出試験結果 (pH5.0, 50rpm)

| 製剤   | ベッセル数 | 時間 (分) |      |       |       |       |       |
|------|-------|--------|------|-------|-------|-------|-------|
|      |       | 5      | 10   | 15    | 30    | 45    | 60    |
| 試験製剤 | 1     | 18.2   | 61.1 | 93.2  | 101.0 | 99.3  | 100.8 |
|      | 2     | 29.3   | 71.5 | 95.6  | 102.9 | 102.5 | 103.7 |
|      | 3     | 17.4   | 55.3 | 82.1  | 101.8 | 102.4 | 103.3 |
|      | 4     | 13.4   | 48.9 | 74.3  | 101.3 | 101.6 | 103.9 |
|      | 5     | 8.1    | 39.5 | 66.7  | 101.1 | 97.1  | 101.9 |
|      | 6     | 28.6   | 74.5 | 98.6  | 91.5  | 102.8 | 104.9 |
|      | 7     | 9.0    | 39.5 | 67.0  | 99.1  | 99.6  | 101.2 |
|      | 8     | 31.1   | 74.4 | 96.9  | 103.7 | 104.1 | 103.1 |
|      | 9     | 29.4   | 76.4 | 100.2 | 102.9 | 104.7 | 107.8 |
|      | 10    | 35.9   | 79.7 | 101.0 | 103.4 | 103.3 | 102.8 |
|      | 11    | 29.7   | 76.2 | 96.4  | 103.0 | 103.5 | 104.2 |
|      | 12    | 11.2   | 44.7 | 74.7  | 102.2 | 103.2 | 104.5 |
|      | 平均    |        | 21.8 | 61.8  | 87.2  | 101.2 | 102.0 |
| 標準偏差 |       | 9.9    | 15.5 | 13.3  | 3.3   | 2.2   | 1.9   |
| 標準製剤 | 1     | 25.2   | 58.9 | 85.6  | 98.7  | 100.1 | 101.4 |
|      | 2     | 28.0   | 70.0 | 95.2  | 100.6 | 102.6 | 99.3  |
|      | 3     | 27.7   | 65.7 | 89.8  | 100.4 | 100.8 | 100.7 |
|      | 4     | 30.0   | 69.4 | 92.1  | 99.5  | 101.3 | 101.3 |
|      | 5     | 26.2   | 66.6 | 92.8  | 102.4 | 101.4 | 101.6 |
|      | 6     | 16.9   | 48.9 | 75.9  | 99.1  | 97.5  | 98.9  |
|      | 7     | 38.6   | 81.5 | 99.3  | 98.1  | 100.0 | 98.6  |
|      | 8     | 52.6   | 91.2 | 97.1  | 97.7  | 98.1  | 97.8  |
|      | 9     | 39.6   | 78.0 | 93.7  | 96.6  | 97.5  | 97.1  |
|      | 10    | 32.7   | 73.4 | 94.5  | 97.4  | 97.8  | 98.4  |
|      | 11    | 42.5   | 83.1 | 96.6  | 98.8  | 99.8  | 100.1 |
|      | 12    | 14.6   | 43.9 | 71.7  | 89.9  | 91.1  | 90.5  |
|      | 平均    |        | 31.2 | 69.2  | 90.4  | 98.3  | 99.0  |
| 標準偏差 |       | 10.8   | 13.8 | 8.6   | 3.1   | 3.0   | 3.0   |

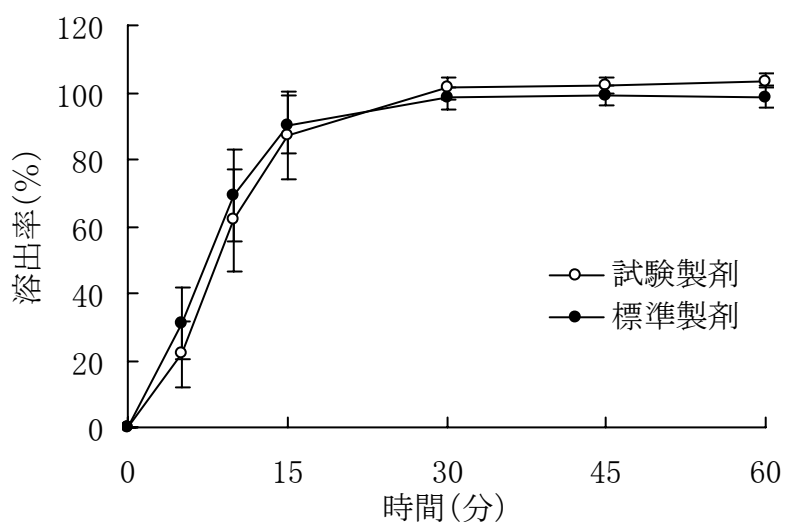


図2 ベニジピン塩酸塩錠 4mg「タイヨー」の溶出試験結果 (pH5.0, 50rpm)

表3 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH6.8, 50rpm)

| 製剤   | ベッセル数 | 時間 (分) |      |      |      |      |      |      |      |      |      |      |      |
|------|-------|--------|------|------|------|------|------|------|------|------|------|------|------|
|      |       | 5      | 10   | 15   | 30   | 45   | 60   | 90   | 120  | 180  | 240  | 300  | 360  |
| 試験製剤 | 1     | 0.0    | 5.2  | 11.1 | 21.5 | 28.5 | 31.4 | 35.8 | 38.5 | 39.5 | 31.8 | 27.2 | 22.8 |
|      | 2     | 0.0    | 4.6  | 10.8 | 23.9 | 29.9 | 33.7 | 36.9 | 39.7 | 39.0 | 31.9 | 26.5 | 29.3 |
|      | 3     | 2.9    | 10.9 | 18.2 | 27.8 | 31.6 | 35.8 | 38.5 | 40.1 | 39.5 | 30.3 | 27.4 | 22.4 |
|      | 4     | 0.0    | 4.5  | 10.1 | 21.8 | 28.1 | 31.7 | 36.3 | 37.5 | 37.0 | 27.5 | 26.0 | 24.7 |
|      | 5     | 0.0    | 5.2  | 11.5 | 24.2 | 29.4 | 34.7 | 37.5 | 40.3 | 41.1 | 30.4 | 29.4 | 24.2 |
|      | 6     | 2.1    | 7.6  | 14.2 | 25.8 | 30.1 | 33.5 | 37.1 | 38.0 | 38.5 | 30.3 | 25.1 | 27.1 |
|      | 7     | 3.1    | 10.4 | 17.2 | 26.5 | 33.0 | 36.3 | 40.5 | 40.7 | 45.1 | 39.3 | 37.3 | 14.9 |
|      | 8     | 1.9    | 8.9  | 16.3 | 28.3 | 34.3 | 37.0 | 40.4 | 42.9 | 45.1 | 40.2 | 38.1 | 16.9 |
|      | 9     | 0.9    | 6.1  | 12.6 | 25.7 | 31.7 | 35.6 | 39.3 | 42.3 | 44.7 | 34.9 | 38.2 | 21.2 |
|      | 10    | 1.8    | 8.1  | 15.4 | 26.9 | 33.5 | 36.8 | 40.1 | 43.8 | 45.4 | 37.7 | 36.6 | 27.1 |
|      | 11    | 0.5    | 5.0  | 9.5  | 24.0 | 31.3 | 34.4 | 39.4 | 43.0 | 43.8 | 36.7 | 35.9 | 24.8 |
|      | 12    | 1.2    | 7.1  | 14.5 | 26.9 | 32.6 | 36.9 | 40.0 | 40.3 | 43.9 | 39.2 | 38.4 | 16.6 |
|      |       | 平均     | 1.2  | 7.0  | 13.5 | 25.3 | 31.2 | 34.8 | 38.5 | 40.6 | 41.9 | 34.2 | 32.2 |
|      | 標準偏差  | 1.1    | 2.2  | 2.9  | 2.2  | 2.0  | 1.9  | 1.7  | 2.0  | 3.1  | 4.3  | 5.6  | 4.5  |
| 標準製剤 | 1     | 8.4    | 19.5 | 26.6 | 36.0 | 37.4 | 41.1 | 38.2 | 39.5 | 29.6 | 24.6 | 18.4 | 15.7 |
|      | 2     | 9.6    | 20.4 | 27.4 | 35.9 | 36.0 | 40.1 | 42.7 | 42.8 | 33.6 | 27.6 | 20.7 | 17.5 |
|      | 3     | 9.8    | 22.0 | 29.5 | 37.5 | 40.8 | 41.9 | 43.7 | 44.3 | 34.4 | 26.9 | 21.0 | 17.6 |
|      | 4     | 8.4    | 20.3 | 29.1 | 37.4 | 40.4 | 42.5 | 42.0 | 41.4 | 31.9 | 24.8 | 20.8 | 17.7 |
|      | 5     | 4.6    | 13.7 | 23.7 | 35.9 | 38.3 | 38.8 | 41.8 | 42.8 | 34.6 | 27.8 | 21.3 | 17.7 |
|      | 6     | 5.5    | 16.0 | 26.0 | 34.1 | 38.7 | 40.0 | 42.0 | 40.9 | 35.4 | 28.0 | 21.6 | 18.9 |
|      | 7     | 7.4    | 19.6 | 28.1 | 36.7 | 41.4 | 44.5 | 46.1 | 45.0 | 44.8 | 24.7 | 17.2 | 11.8 |
|      | 8     | 7.4    | 19.4 | 28.6 | 37.8 | 42.1 | 44.6 | 46.9 | 44.1 | 42.7 | 22.8 | 15.8 | 11.6 |
|      | 9     | 5.3    | 16.3 | 24.8 | 35.2 | 40.6 | 43.8 | 45.7 | 44.8 | 42.9 | 20.8 | 15.7 | 11.9 |
|      | 10    | 4.2    | 14.1 | 22.0 | 34.6 | 39.8 | 43.4 | 44.4 | 45.0 | 42.1 | 20.1 | 14.9 | 11.2 |
|      | 11    | 6.2    | 17.3 | 26.5 | 36.8 | 41.3 | 44.2 | 45.8 | 46.1 | 43.0 | 20.8 | 15.3 | 11.5 |
|      | 12    | 7.7    | 19.7 | 29.0 | 38.5 | 42.1 | 45.0 | 47.1 | 46.7 | 44.5 | 20.3 | 15.5 | 11.5 |
|      |       | 平均     | 7.0  | 18.2 | 26.8 | 36.4 | 39.9 | 42.5 | 43.9 | 43.6 | 38.3 | 24.1 | 18.2 |
|      | 標準偏差  | 1.9    | 2.7  | 2.3  | 1.3  | 1.9  | 2.1  | 2.6  | 2.2  | 5.5  | 3.1  | 2.7  | 3.2  |

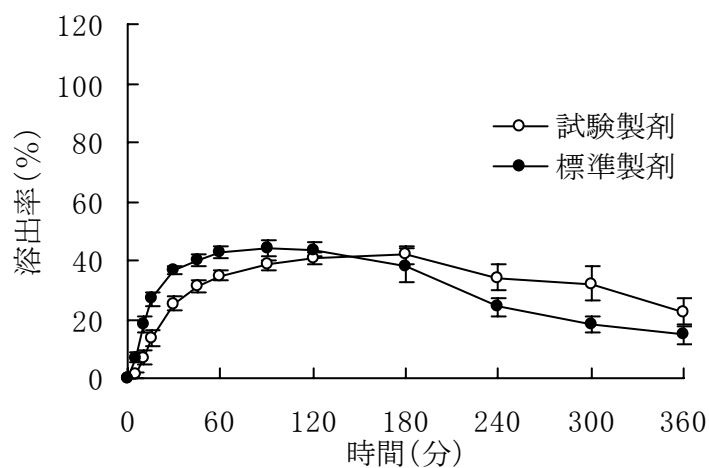


図3 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH6.8, 50rpm)

表4 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果（水，50rpm）

| 製剤   | ベッセル数 | 時間（分） |      |      |      |      |      |      |      |       |      |      |      |
|------|-------|-------|------|------|------|------|------|------|------|-------|------|------|------|
|      |       | 5     | 10   | 15   | 30   | 45   | 60   | 90   | 120  | 180   | 240  | 300  | 360  |
| 試験製剤 | 1     | 5.7   | 19.9 | 33.1 | 54.3 | 61.5 | 71.2 | 83.3 | 87.6 | 84.6  | 82.0 | 83.9 | 78.2 |
|      | 2     | 5.6   | 23.9 | 40.5 | 63.8 | 73.0 | 80.9 | 77.3 | 82.0 | 102.4 | 93.0 | 92.1 | 88.6 |
|      | 3     | 7.0   | 27.3 | 44.9 | 67.1 | 75.7 | 80.7 | 79.0 | 82.9 | 93.8  | 89.0 | 86.7 | 79.1 |
|      | 4     | 4.2   | 17.8 | 31.5 | 55.9 | 66.3 | 72.6 | 85.9 | 89.1 | 84.1  | 81.7 | 81.7 | 77.7 |
|      | 5     | 5.4   | 20.2 | 33.3 | 55.0 | 65.3 | 70.7 | 86.6 | 90.3 | 83.6  | 82.9 | 83.8 | 80.5 |
|      | 6     | 9.9   | 28.6 | 44.8 | 64.6 | 72.8 | 79.0 | 78.1 | 83.2 | 90.6  | 88.6 | 89.8 | 86.2 |
|      | 7     | 5.8   | 22.0 | 36.4 | 57.9 | 69.2 | 73.8 | 76.8 | 82.0 | 85.0  | 86.6 | 83.7 | 92.6 |
|      | 8     | 6.8   | 24.7 | 41.1 | 63.0 | 72.1 | 76.8 | 83.0 | 87.5 | 89.1  | 91.1 | 92.8 | 94.6 |
|      | 9     | 6.9   | 24.6 | 40.1 | 67.2 | 74.6 | 80.4 | 87.1 | 89.7 | 90.6  | 88.0 | 94.1 | 97.4 |
|      | 10    | 5.6   | 21.8 | 38.1 | 61.5 | 70.3 | 76.6 | 81.9 | 87.5 | 88.4  | 91.0 | 93.3 | 97.2 |
|      | 11    | 9.1   | 31.0 | 48.2 | 69.2 | 76.3 | 80.5 | 87.5 | 89.0 | 91.7  | 93.0 | 95.8 | 95.5 |
|      | 12    | 4.7   | 20.2 | 36.0 | 59.6 | 71.5 | 77.1 | 82.7 | 85.2 | 88.5  | 87.5 | 89.7 | 95.7 |
|      |       | 平均    | 6.4  | 23.5 | 39.0 | 61.6 | 70.7 | 76.7 | 82.4 | 86.3  | 89.4 | 87.9 | 89.0 |
|      | 標準偏差  | 1.7   | 4.0  | 5.2  | 5.1  | 4.5  | 3.8  | 3.9  | 3.1  | 5.2   | 4.0  | 4.8  | 7.9  |
| 標準製剤 | 1     | 19.8  | 45.1 | 72.4 | 76.2 | 83.9 | 87.5 | 87.1 | 89.2 | 84.5  | 79.0 | 82.5 | 76.8 |
|      | 2     | 8.8   | 29.1 | 45.6 | 66.1 | 76.1 | 80.2 | 90.7 | 77.9 | 82.8  | 79.4 | 77.7 | 74.4 |
|      | 3     | 25.6  | 53.8 | 76.9 | 81.7 | 88.6 | 90.6 | 88.4 | 89.6 | 89.2  | 86.4 | 87.0 | 85.3 |
|      | 4     | 18.9  | 44.3 | 72.2 | 82.3 | 88.2 | 91.5 | 91.3 | 83.9 | 87.1  | 89.3 | 87.2 | 85.2 |
|      | 5     | 12.6  | 29.5 | 53.0 | 69.1 | 78.1 | 79.3 | 80.8 | 82.9 | 80.1  | 79.4 | 76.9 | 74.6 |
|      | 6     | 23.0  | 47.1 | 74.2 | 81.5 | 85.0 | 89.0 | 90.7 | 88.1 | 87.8  | 88.3 | 86.8 | 85.4 |
|      | 7     | 25.9  | 62.9 | 73.4 | 87.0 | 88.2 | 88.0 | 89.8 | 87.1 | 82.9  | 83.3 | 82.2 | 84.5 |
|      | 8     | 21.3  | 48.9 | 71.6 | 84.9 | 85.7 | 87.4 | 85.9 | 83.9 | 79.4  | 83.2 | 82.9 | 84.9 |
|      | 9     | 12.8  | 45.2 | 65.5 | 85.0 | 91.6 | 87.8 | 90.9 | 90.9 | 87.9  | 88.2 | 83.9 | 88.7 |
|      | 10    | 21.6  | 52.2 | 70.8 | 85.2 | 90.1 | 87.2 | 85.9 | 87.5 | 82.5  | 85.6 | 84.3 | 86.6 |
|      | 11    | 19.5  | 48.7 | 67.8 | 81.8 | 87.6 | 88.2 | 88.7 | 84.0 | 80.9  | 84.2 | 84.0 | 85.3 |
|      | 12    | 19.6  | 50.1 | 72.4 | 85.9 | 90.1 | 90.2 | 92.7 | 91.9 | 87.0  | 89.6 | 84.1 | 89.1 |
|      |       | 平均    | 19.1 | 46.4 | 68.0 | 80.6 | 86.1 | 87.2 | 88.6 | 86.4  | 84.3 | 84.7 | 83.3 |
|      | 標準偏差  | 5.3   | 9.4  | 9.3  | 6.7  | 4.8  | 3.8  | 3.3  | 4.0  | 3.4   | 3.9  | 3.3  | 5.1  |

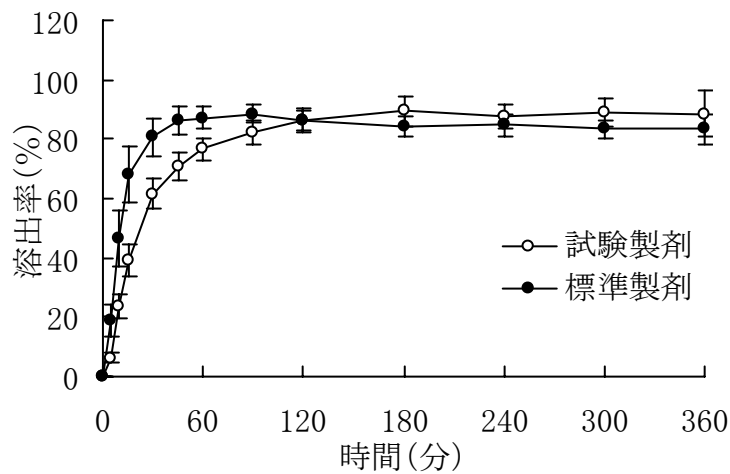


図4 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果（水，50rpm）

表5 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH1.2, 100rpm)

| 製剤   | ベッセル数 | 時間 (分) |       |       |       |
|------|-------|--------|-------|-------|-------|
|      |       | 5      | 10    | 15    | 30    |
| 試験製剤 | 1     | 45.1   | 95.7  | 107.2 | 107.4 |
|      | 2     | 67.1   | 106.5 | 105.3 | 107.9 |
|      | 3     | 66.9   | 103.2 | 109.6 | 107.8 |
|      | 4     | 52.2   | 100.4 | 108.8 | 107.1 |
|      | 5     | 53.8   | 89.7  | 106.6 | 107.8 |
|      | 6     | 45.5   | 85.2  | 109.3 | 107.3 |
|      | 7     | 44.7   | 85.9  | 102.5 | 104.8 |
|      | 8     | 56.9   | 91.9  | 105.3 | 105.4 |
|      | 9     | 23.4   | 55.5  | 84.3  | 105.5 |
|      | 10    | 45.9   | 92.3  | 104.3 | 99.6  |
|      | 11    | 25.7   | 65.6  | 90.9  | 102.3 |
|      | 12    | 27.0   | 67.8  | 94.0  | 92.6  |
|      | 平均    |        | 46.2  | 86.6  | 102.3 |
| 標準偏差 |       | 14.7   | 15.9  | 8.2   | 4.6   |
| 標準製剤 | 1     | 55.7   | 97.7  | 98.5  | 95.3  |
|      | 2     | 66.8   | 94.6  | 93.2  | 95.2  |
|      | 3     | 46.3   | 83.8  | 98.9  | 100.3 |
|      | 4     | 43.4   | 78.0  | 97.8  | 103.0 |
|      | 5     | 55.5   | 88.9  | 98.3  | 97.1  |
|      | 6     | 49.3   | 89.7  | 96.7  | 98.5  |
|      | 7     | 40.3   | 76.4  | 100.1 | 96.1  |
|      | 8     | 90.9   | 97.2  | 95.5  | 98.2  |
|      | 9     | 68.9   | 92.9  | 101.9 | 103.1 |
|      | 10    | 56.0   | 86.7  | 99.7  | 99.2  |
|      | 11    | 62.0   | 99.4  | 101.4 | 103.1 |
|      | 12    | 43.3   | 80.7  | 97.1  | 100.5 |
|      | 平均    |        | 56.5  | 88.8  | 98.3  |
| 標準偏差 |       | 14.3   | 7.9   | 2.5   | 2.9   |

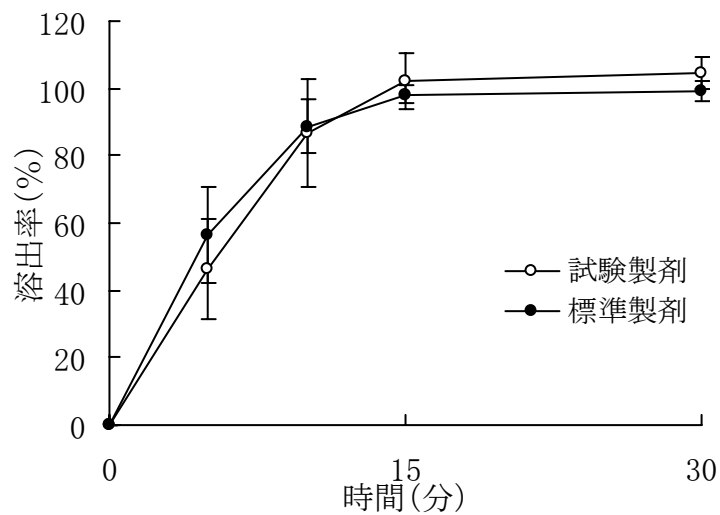


図5 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH1.2, 100rpm)

## 結論

溶出試験の結果より試験製剤と標準製剤の平均溶出率を比較したところ、50rpm の pH1.2、pH4.0 及び 100rpm の pH1.2 では基準に適合したが、50rpm の pH6.8 及び水では基準に適合しなかった。生物学的同等性試験ガイドラインにおいて、この差は「著しい差」ではなく、また、「溶出試験の同等性の判定は生物学的に同等であることを意味するものではない」と述べられている。今回、当該製剤の体内薬物動態を確認したところ、両製剤は生物学的に同等である結果が得られた。従って、この溶出試験結果の違いは、血中濃度に反映されず問題ないものである。