

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No.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No.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°C

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。

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。

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 |

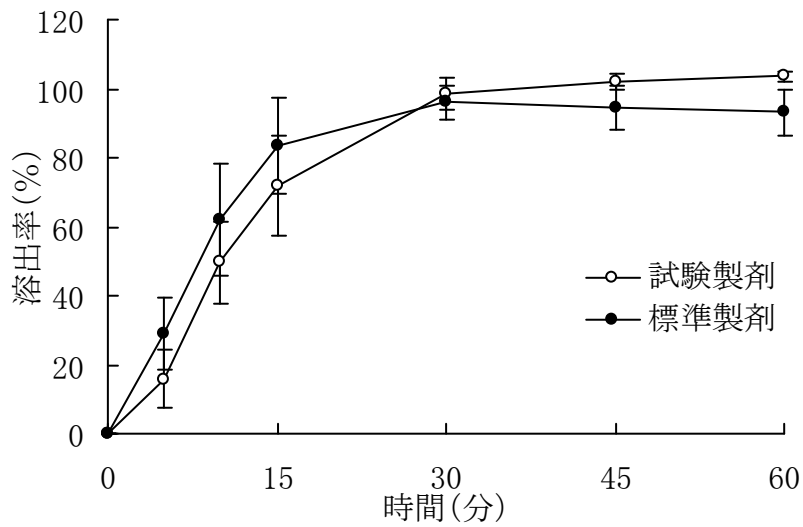


図1 ベニジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH1.2, 50rpm)

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 |

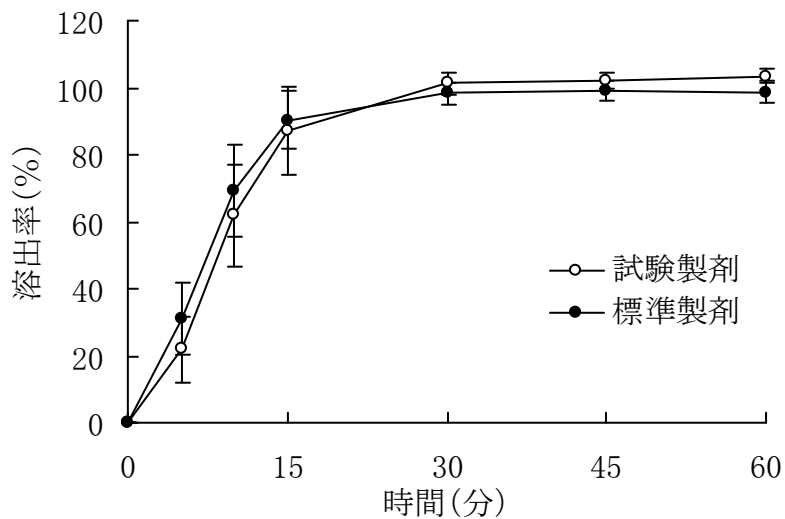


図2 ベニジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH5.0, 50rpm)

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 |

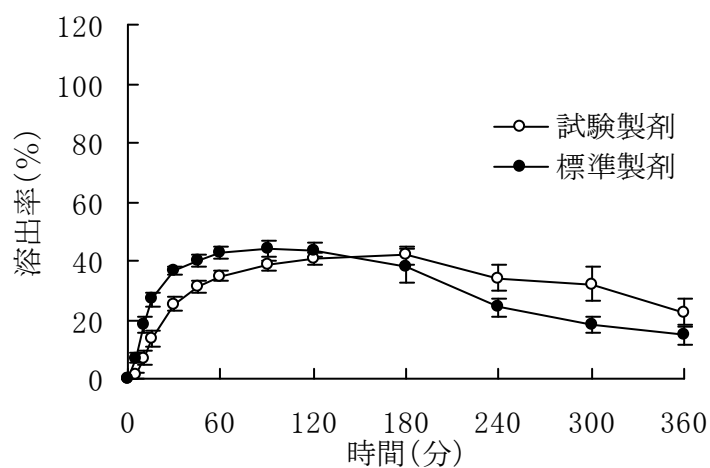


図3 ベンジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (pH6.8, 50rpm)

表4 ベニジピン塩酸塩錠 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 |

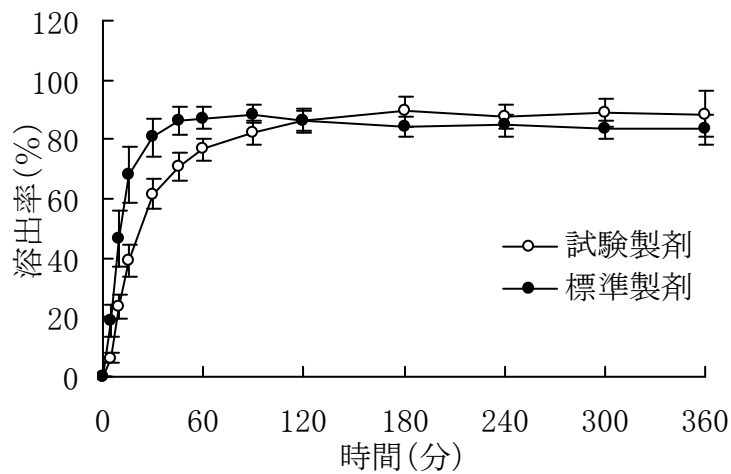


図4 ベニジピン塩酸塩錠 4mg 「タイヨー」の溶出試験結果 (水, 50rpm)

表5 ベニジピン塩酸塩錠 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 |

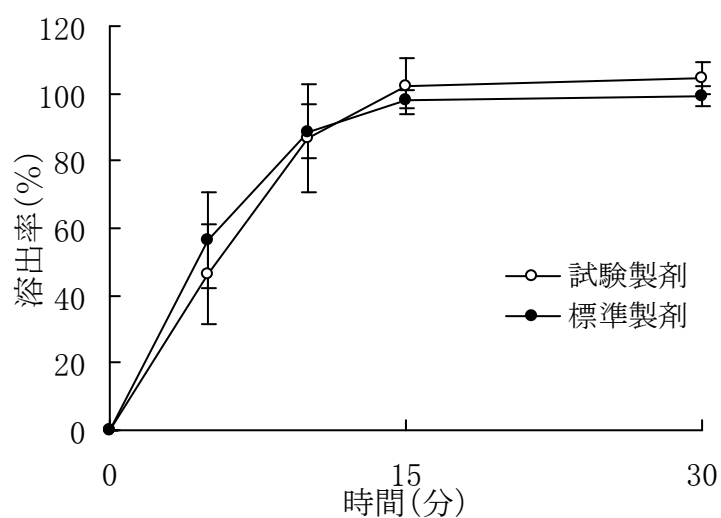


図5 ベニジピン塩酸塩錠 4mg 「タイヨー」 の溶出試験結果 (pH1.2, 100rpm)