



Research Article

Design, Development and Evaluation of Bilayer Tablet for Antihypertension Activity

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ABSTRACT

In the present study we have prepared bilayer matrix of atorvastatin immediate release and atenolol sustained release tablet. Atorvastatin immediate release layer composed of high amount of starch while atenolol sustained release layer contains high amount of Kollidon SR and MCC pH 102. The *in vitro* drug release of prepared bilayered tablet (FT) was measured and compared with marketed tablet of sustained release Atenolol tablet (NOLWIS; Smayan Healthcare Pvt Ltd) which showed fast release of atorvastatin within 45 seconds and sustained release of atenolol over a period of more than 24 hrs. However, the marketed table showed complete drug release within 14 hrs. These results revealed that the prepared bilayer tablet have fast releasing ability of atorvastatin and sustained release profile of atenolol.

INTRODUCTION

Hypertension is a foremost health issue around the world due to its high incidence and relationship with an elevated risk of cardiovascular disease^[1,2]. Developments in hypertension detection and treatment have contributed significantly to the remarkable decreases in heart disease and stroke mortality in developed countries. Nevertheless, in many of these countries, high blood pressure control rates have slowed in recent years^[3,4].

The major pharmacological classes used to decrease blood pressure are: β -blockers, diuretics, ACE-inhibitors, Calcium antagonists, Angiotensin-II antagonists and α -adrenergic blockers.

Drug administration in standard dosage forms necessitates a large dose, frequent administration, and a short time, all of which increase the risk of toxicity^[5,6]. While in controlled drug delivery devices, the medicine is used efficiently, for an extended period of time, with very minimal risk of toxicity, allowing for increased patient complications and better therapeutic management. Bi-layer tablets represent a new era in the successful creation of controlled release formulations, as well as various qualities that contribute to a successful drug delivery system^[7]. Bi-layer tablets are appropriate for sequential release of two medications in combination, separating two incompatible substances, and for sustained

release tablets in which one layer is immediate release as the first dose and the second layer is maintenance dose [8,9].

The aim of the present investigation is to formulate a bilayer tablet of the two drugs. Atenolol is chosen to be as sustained release as it has a short half-life of 6 hours which therefore, has to be administered several times a day causing drug plasma level fluctuations and further adverse effects. Atorvastatin calcium has a long half-life of 14 h, therefore requires administration once a day and hence was chosen as the immediate release layer. The work aimed to optimise a tablet that will release atorvastatin within 1 hour and sustain the release of atenolol upto 24 hours using novel directly compressible excipients which not only helps in manufacturing ease but most importantly will improve therapeutic efficacy and patient compliance.

MATERIALS AND METHODS

Materials

Ethyl cellulose 22 CPS USP/EP, Eudragit RL and RS 100 were purchased from Signet Chemical Corporation, India. Sun Pharmaceutical Ind. Ltd., India and Wanbury Ltd., Mumbai generously supplied atenolol and atorvastatin as a gift sample respectively. Polyvinyl pyrrolidone, triethanol amine and propylene glycol was procured from Loba Chemical Pvt. Ltd., Mumbai, India. Ethylene vinyl acetate copolymer, pregelatinized starch was purchased from

Aldrich Chemicals, U.K.. All other chemicals were of analytical reagent grade.

Methods

Bilayer matrix tablets contained two layers i.e. first layer consists of the optimized immediate release blend of atorvastatin and second layer, the sustained release layer of Atenolol. The immediate release layer of atorvastatin calcium was prepared using directly compressible diluent microcrystalline cellulose pH 102 (Avicel 102), superdisintegrant, SLS as solubilizer, lactose as diluent, calcium carbonate as stabilizer, colloidal silicon dioxide (aerosil) as glidant and magnesium stearate as lubricant (Table 1).

Precompression characteristics of trial batches of immediate release atorvastatin calcium blends were determined. Precompression parameters including bulk density, tapped density, Carr's index, angle of repose, Hausner ratio were determined for all the formulations of atorvastatin calcium immediate release were represented in Table 2.

The preliminary trial batches of immediate release tablets of atorvastatin calcium were subjected to *in vitro* release using USP type II paddle dissolution apparatus using 900 ml phosphate buffer pH 6.8 at 50 rpm at 37±0.5°C for one hour, the samples being withdrawn at intervals of 5, 10, 15, 30, 45 and 60 minutes and the results are depicted in Table 4. The *in vitro* release data suggests that among the three disintegrants starch showed the best drug release.

Table 1: Composition of atorvastatin calcium immediate release blends.

| Ingredients (mg) | Formulation | | | | | | | | |
|-----------------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Atorvastatin | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Crospovidone | 5 | 10 | 15 | | | | | | |
| Starch (soluble) | | | | 5 | 10 | 15 | | | |
| Croscarmellose sodium | | | | | | | 5 | 10 | 15 |
| SLS | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| MCC pH 102 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Lactose | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Calcium Carbonate | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Magnesium stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total weight | 100 | 105 | 110 | 100 | 105 | 110 | 100 | 105 | 110 |

Table 2: Evaluation of atorvastatin immediate release layer trial batches blends.

| Formulation Code | Bulk (gm/cc) | Density Tapped (gm/cc) | Density (gm/cc) | Angle of Repose (θ) | Carr's Index (%) | Hausner Ratio |
|------------------|--------------|------------------------|-----------------|---------------------|------------------|---------------|
| F1 | 0.40±0.07 | 0.52±0.07 | | 21.47±0.46 | 15.29 | 1.17 |
| F2 | 0.39±0.07 | 0.50±0.08 | | 22.51±0.43 | 14.44 | 1.14 |
| F3 | 0.42±0.08 | 0.53±0.08 | | 21.34±0.50 | 14.21 | 1.14 |
| F4 | 0.43±0.09 | 0.47±0.09 | | 22.37±0.49 | 15.56 | 1.17 |
| F5 | 0.46±0.06 | 0.49±0.09 | | 22.42±0.51 | 15.32 | 1.16 |
| F6 | 0.45±0.07 | 0.51±0.06 | | 23.23±0.43 | 14.64 | 1.17 |
| F7 | 0.41±0.07 | 0.52±0.07 | | 21.45±0.24 | 14.54 | 1.17 |
| F8 | 0.43±0.08 | 0.49±0.08 | | 22.23±0.54 | 13.54 | 1.16 |
| F9 | 0.42±0.06 | 0.48±0.08 | | 22.34±0.43 | 14.65 | 1.19 |

All values are expressed as mean± SD; (n=3)

Table 3: Evaluation of atorvastatin immediate release layer trial batches tablets.

| Formulation Code | Average hardness (kg/cm ²) | Weight Variation (mg) | Average friability (% w/w) | Disintegration time (sec) | Drug content (%) |
|------------------|----------------------------------------|-----------------------|----------------------------|---------------------------|------------------|
| F1 | 3.94±0.14 | 100±0.72 | 0.56±0.007 | 54±2 | 99.44±0.58 |
| F2 | 3.54±0.23 | 105±0.58 | 0.58±0.006 | 52±2 | 98.63±0.51 |
| F3 | 3.45±0.53 | 110±0.57 | 0.71±0.008 | 50±3 | 99.34±0.62 |
| F4 | 3.64±0.64 | 100±0.28 | 0.53±0.005 | 55±2 | 99.68±0.69 |
| F5 | 3.47±0.46 | 105±0.48 | 0.61±0.004 | 50±2 | 99.21±0.43 |
| F6 | 3.65±0.54 | 110±0.98 | 0.74±0.007 | 45±3 | 98.99±0.88 |
| F7 | 3.66±0.35 | 100±0.34 | 0.52±0.008 | 54±2 | 99.32±0.33 |
| F8 | 3.57±0.46 | 105±0.75 | 0.64±0.006 | 50±3 | 99.76±0.38 |
| F9 | 3.54±0.47 | 110±0.35 | 0.69±0.007 | 52±2 | 99.37±0.13 |

All values are expressed as mean± SD; (n=3)

Table 4: *In vitro* release of atorvastatin immediate release trial batches tablets

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|------------|------------|------------|-------------|------------|------------|------------|------------|------------|------------|
| 5 | 17.50±1.34 | 19.34±1.34 | 21.32±1.32 | 17.23±1.33 | 15.32±1.98 | 30.25±1.53 | 18.57±1.83 | 17.28±1.73 | 21.54±1.93 |
| 10 | 27.51±1.68 | 30.65±1.68 | 33.81±1.53 | 26.87±1.21 | 23.53±1.84 | 42.64±1.37 | 26.27±1.38 | 30.85±1.85 | 30.20±1.53 |
| 15 | 49.95±1.72 | 46.64±1.72 | 51.34±1.73 | 41.24±1.52 | 39.26±1.92 | 55.22±1.98 | 37.69±1.23 | 40.45±1.38 | 40.73±1.92 |
| 30 | 63.84±1.13 | 66.13±1.13 | 73.42±1.22 | 60.54±1.43 | 56.37±1.26 | 94.64±1.36 | 57.82±1.44 | 59.29±1.85 | 60.54±1.53 |
| 45 | 86.19±1.53 | 87.16±1.53 | 87.72±1.43 | 81.43±1.76 | 78.43±1.43 | 99.41±1.28 | 79.54±1.47 | 84.49±1.33 | 80.93±1.05 |
| 60 | 97.52±1.92 | 99.42±1.92 | 100.00±0.52 | 96.38±1.83 | 90.67±2.49 | 99.73±1.85 | 96.34±1.25 | 99.82±1.85 | 99.92±0.94 |

After preliminary screening of various polymers, Kollidon SR and Eudragit RS 100 were chosen as release retardants for the sustained release layer of atenolol. Various trial batches were

taken to ascertain the concentration range of Kollidon SR, the effect of Eudragit RS on drug release and to ascertain the concentration of diluent MCC pH102 as depicted in Table 5.

Table 5: Preliminary screening of atenolol sustained release blends.

| Ingredients (mg) | Formulation | | | | | | | | |
|--------------------|-------------|-----|-----|----|-----|-----|-----|-----|-----|
| | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 |
| Atenolol | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Kollidon SR | 25 | 30 | 35 | 15 | 20 | 30 | 20 | 25 | 30 |
| Eudragit RS 100 | 5 | 10 | 15 | 5 | 10 | 15 | 5 | 10 | 20 |
| MCC pH 102 | 18 | 23 | 23 | 18 | 18 | 23 | 23 | 23 | 23 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total weight | 100 | 115 | 125 | 90 | 100 | 120 | 100 | 100 | 125 |

Table 6: Precompression characteristics of Preliminary trial batches of sustained release atenolol succinate

| Formulation Code | Bulk (gm/cc) | Density (gm/cc) | Tapped Density (gm/cc) | Angle of Repose (θ) | Carr's Index (%) | Hausner Ratio |
|------------------|--------------|-----------------|------------------------|------------------------------|------------------|---------------|
| T1 | 0.34±0.08 | 0.59±0.08 | 0.59±0.08 | 20.64±0.35 | 14.54 | 1.05 |
| T2 | 0.43±0.07 | 0.47±0.07 | 0.47±0.07 | 21.57±0.67 | 15.35 | 1.24 |
| T3 | 0.42±0.06 | 0.53±0.08 | 0.53±0.08 | 22.75±0.47 | 16.54 | 1.17 |
| T4 | 0.32±0.08 | 0.44±0.07 | 0.44±0.07 | 21.46±0.84 | 14.35 | 1.15 |
| T5 | 0.46±0.07 | 0.42±0.07 | 0.42±0.07 | 22.54±0.36 | 12.35 | 1.16 |
| T6 | 0.47±0.08 | 0.57±0.07 | 0.57±0.07 | 21.76±0.75 | 14.74 | 1.14 |
| T7 | 0.45±0.07 | 0.54±0.08 | 0.54±0.08 | 20.64±0.63 | 14.35 | 1.16 |
| T8 | 0.48±0.08 | 0.57±0.07 | 0.57±0.07 | 20.35±0.53 | 16.35 | 1.13 |
| T9 | 0.46±0.06 | 0.48±0.07 | 0.48±0.07 | 20.33±0.36 | 16.73 | 1.24 |

All values are expressed as mean± SD; (n=3)

Table 7: Post compression characteristics of preliminary trial batches of sustained release atenolol succinate.

| Formulation Code | Average hardness (kg/cm ²) | Weight Variation | Average friability (% w/w) | Drug content (%) |
|------------------|----------------------------------------|------------------|----------------------------|------------------|
| T1 | 6.54±0.12 | 100±0.62 | 0.35±0.007 | 98.67±0.58 |
| T2 | 6.64±0.13 | 115±0.38 | 0.24±0.006 | 94.63±0.51 |
| T3 | 5.78±0.43 | 120±0.37 | 0.53±0.008 | 98.34±0.62 |
| T4 | 5.79±0.21 | 90±0.43 | 0.35±0.005 | 98.68±0.69 |
| T5 | 5.99±0.23 | 100±0.65 | 0.25±0.004 | 99.51±0.43 |
| T6 | 6.53±0.43 | 120±0.34 | 0.56±0.007 | 98.54±0.88 |
| T7 | 6.66±0.24 | 100±0.64 | 0.35±0.008 | 99.64±0.33 |
| T8 | 6.54±0.43 | 100±0.45 | 0.66±0.006 | 99.46±0.38 |
| T9 | 6.32±0.24 | 125±0.33 | 0.35±0.007 | 98.67±0.13 |

All the precompression parameters indicate good packing property and flowability of the trial blends T1–T9 of atenolol succinate. Post compression characteristics of all batches T1–T9 were evaluated; the results are indicated in Table 7. The *in vitro* drug release of the trial formulations of metoprolol succinate sustained release layer (T1–T9) is tabulated in Table 8.

The best batch of immediate release layer of atorvastatin calcium (F6) was selected and was compressed with sustained release atenolol (T3) as shown in Table 9. The blends of atenolol succinate sustained release were evaluated for precompression characteristics. The weight of the bilayered tablet was 235 mg. The bilayered tablets were further evaluated for post compression characteristics.

Table 8: *In vitro* drug release of atenolol sustained release tablets (T1-T9).

| Time (Hr) | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 |
|-----------|----------|----------|----------|-----------|----------|----------|-----------|-----------|----------|
| 2 | 20.3±2.7 | 22.4±1.7 | 14.4±2.3 | 24.6±1.7 | 21.2±1.3 | 18.2±1.9 | 19.7±1.7 | 27.9±1.7 | 23.6±1.4 |
| 4 | 34.2±2.5 | 37.2±2.2 | 21.2±1.8 | 39.6±1.5 | 28.4±1.6 | 25.5±1.8 | 27.8±2.3 | 40.1±1.5 | 37.3±1.5 |
| 6 | 45.6±1.2 | 42.2±2.3 | 28.2±1.6 | 50.6±2.2 | 39.5±2.4 | 34.7±1.5 | 38.6±2.2 | 61.1±2.2 | 52.6±2.3 |
| 8 | 56.4±2.8 | 58.7±2.2 | 36.7±2.2 | 61.7±1.8 | 50.2±1.7 | 49.7±1.5 | 47.4±1.6 | 76.1±1.8 | 63.3±1.2 |
| 10 | 63.3±2.4 | 69.5±2.5 | 44.5±2.4 | 71.8±2.4 | 63.1±2.4 | 60.6±2.3 | 56.2±2.4 | 91.2±2.4 | 75.2±2.4 |
| 12 | 74.4±2.6 | 80.3±2.3 | 55.3±1.6 | 84.8±1.6 | 78.3±2.2 | 73.5±2.2 | 64.6±1.5 | 99.2±1.6 | 87.3±2.4 |
| 14 | 89.6±1.5 | 96.8±1.7 | 63.8±2.2 | 93.6±1.5 | 91.5±2.2 | 88.5±2.2 | 73.2±2.4 | 100.2±1.8 | 98.5±2.3 |
| 16 | 92.4±2.9 | 99.5±1.8 | 70.5±2.1 | 99.3±1.9 | 99.7±1.1 | 96.4±1.2 | 91.5±2.3 | 100.2±1.8 | 99.7±1.4 |
| 18 | 99.2±1.6 | 99.6±1.6 | 77.6±2.2 | 100.3±1.6 | 99.4±1.6 | 99.7±2.4 | 98.3±1.6 | 99.6±1.6 | 99.4±1.7 |
| 20 | 99.7±2.6 | 98.4±2.6 | 82.4±2.5 | 99.2±1.6 | 99.2±2.4 | 98.8±2.2 | 100.3±1.8 | 97.6±1.6 | 98.3±2.4 |
| 22 | 98.4±2.9 | 97.8±2.7 | 89.8±2.4 | 99.3±1.9 | 98.5±1.5 | 97.5±1.7 | 98.2±2.4 | 94.4±1.9 | 98.7±1.3 |
| 24 | 97.3±2.7 | 96.7±2.5 | 92.7±2.2 | 98.3±2.2 | 97.4±1.6 | 95.2±1.8 | 97.7±1.4 | 92.1±2.2 | 97.7±1.6 |

Table 9: Composition of bilayered tablets of atorvastatin immediate release and atenolol succinate sustained release (FT).

| Formulation Code | Composition of immediate release Atorvastatin | | | | | | | |
|---------------------------------|-----------------------------------------------|------------------|-------------|-----------------|------------|--------------------|--------------------|-------------------|
| | Atorvastatin | Starch (soluble) | SLS | MCC pH 102 | Lactose | Calcium Carbonate | Magnesium stearate | Total Weight (mg) |
| F6 | 10 | 15 | 1 | 25 | 50 | 8 | 1 | 110 |
| T3 | Atenolol | | Kollidon SR | Eudragit RS 100 | MCC pH 102 | Magnesium stearate | Total Weight (mg) | |
| | 50 | | 35 | 15 | 23 | 2 | 125 | |
| Total Tablet weight (mg) | | | | | 235 | | | |

Table 10: Post compression characteristics of bilayered tablets of atenolol succinate and atorvastatin calcium.

| Formulation Code | Hardness (kg/cm ²) | Weight Variation | Friability (% w/w) | Drug content (%) | Drug Content (Atorvastatin %) | Drug Content (Atenolol %) |
|------------------|--------------------------------|------------------|--------------------|------------------|-------------------------------|---------------------------|
| FT | 5.87±0.32 | 235±1.52 | 0.29±0.006 | 98.67±0.58 | 98.99±0.83 | 98.34±0.63 |

Table 11: *In vitro* drug release of bilayered tablets (FT) and marketed tablet of sustained release atenolol succinate.

| | Time (Min) | | | | | |
|-------------------------------|------------|------------|------------|------------|------------|------------|
| | 5 | 10 | 15 | 30 | 45 | 60 |
| Atorvastatin (% Drug Release) | 29.62±1.73 | 40.72±1.27 | 54.88±1.82 | 82.38±1.56 | 99.62±1.28 | 99.99±1.72 |
| | Time (Hr) | | | | | |
| | 2 | 4 | 10 | 14 | 18 | 24 |
| Atenolol (% Drug Release) | 12.62±2.15 | 20.72±1.98 | 43.63±2.73 | 60.77±2.12 | 76.62±2.12 | 90.53±2.19 |
| | Time (Hr) | | | | | |
| | 2 | 4 | 10 | 14 | 18 | 24 |
| Market Formulation (NOLWIS) | 18.45±1.35 | 31.46±1.75 | 82.62±1.83 | 98.82±1.73 | 96.38±1.64 | 90.52±2.01 |

RESULTS AND DISCUSSION

Total nine blends (F1-F9) were prepared for atorvastatin calcium immediate release by changing formulations. The bulk densities of atorvastatin calcium immediate release trial formulations were in the range of 0.39 to 0.46 g/cm³. The tapped densities were 0.47 to 0.53 g/cm³. These results confirm that the blends had good packing capacity. The values of Carr's index for all the formulations of atorvastatin calcium immediate release layer ranged from 13.54% to 15.29%. The Carr's index values for the preliminary trial batches of immediate release were less than 16% which indicated good flow. The Hausner ratios were ranged from 1.14 to 1.19. The values of Hausner ratio of all blends was below 1.25 which indicated an excellent flow property for all the formulations of atorvastatin calcium immediate release preliminary trial batches. The angle of repose ranged from 21.34 to 23.23 for all the preliminary trial formulations of immediate release layer, which indicate good flow properties.

The preliminary trial batches F1-F9, after compression were subjected for post compression characteristics like hardness, weight variation, friability, thickness, disintegration time, drug content uniformity and *in vitro* dissolution. The hardness of the tablets ranges from 3.45–3.94kg/cm³ and all the batches showed uniform thickness. Weight variations for all the preliminary trial formulations of atorvastatin calcium immediate release tablets were found to be within the acceptable range of 10%.

The % drug content for all formulations of atorvastatin calcium immediate release tablets were found in the range of 98.63±0.51% to 99.76±0.38% and within the acceptable limits which assured good drug content uniformity among the tablets. The disintegration time for all the trial formulations were almost 60 seconds, however formulation F6 showed highest disintegration rate and showed almost disintegration within 45 seconds. Due to highest disintegration time formulation F6 was selected for bilayer matrix tablet. Formulation F6 contains highest starch level, which may be responsible for fast disintegration.

Similar to Atorvastatin calcium immediate release tablet, Atenolol sustained released tablets were also prepared by changing formulations. Total nine (T1-T9) formulations were prepared and the loose bulk densities of atenolol sustained released trial formulations were found in the range of 0.32 to 0.48 g/cm³. The tapped densities were found to be in between 0.42 to 0.59 g/cm³. The values of Carr's index for all the formulations of Atenolol sustained release layer ranged from 12.35% to 16.73%. In all formulations, the Hausner ratios were ranged from 1.14 to 1.19. The values of Hausner ratio of all blends was below 1.25 which indicated an excellent flow property that was observed for all the formulations of atorvastatin calcium immediate release preliminary trial batches. The angle of repose of all formulations ranged from 20.33 to 22.75 for all the preliminary trial formulations of immediate release layer, which indicate good flow properties. The average hardness of the sustained release layer was between 5.78–6.66 kg/cm². All the batches showed uniform thickness. Weight variations for all the preliminary trial formulations of atenolol succinate sustained release tablets were found to be within the acceptable range of 7.5%. The % of drug content was found within the acceptable limits for all formulations.

Table 8, *in vitro* sustained release tablet showed that all the formulations showed sustained drug release and showed almost drug release within 16 hrs. However formulation T3 will released almost drug within 24 hrs. Since formulation T3 released showed drug release hence consider for bilayer matrix tablet. Tablet T3 contains highest amount of Kollidon SR and MCC pH 102 which may be possible reason for sustained drug release.

On the basis of above outcomes, the best batch of immediate release layer of atorvastatin calcium (F6) was selected and was compressed with sustained release atenolol (T3). The blends of atenolol succinate sustained release were evaluated for precompression characteristics. The weight of the bilayered tablet was 235 mg.

The hardness of bilayer tablet was 5.87±0.32 kg/cm², friability 0.29±0.006, atorvastatin contains 98.99±0.83 and atenolol contains 98.34±0.63. The total drug contains was 98.67±0.58.

In vitro drug release of prepared bilayered tablet (FT) was measured and compared with marketed tablet of sustained release atenolol tablet (NOLWIS; Smayan Healthcare Pvt Ltd). Results revealed fast release of atorvastatin within 45 seconds and sustained release of atenolol over a period of more than 24 hrs. Whereas the marketed tablet showed complete drug release within 14 hrs. These results revealed that the prepared bilayer tablet have fast releasing ability of atorvastatin and sustained release profile of atenolol.

CONCLUSION

A dual drug combination of compressed drugs was reported in the present study. Prepared tablet showed immediate release of atorvastatin and sustained release of atenolol. Prepared bilayer tablet showed remarkable approach for the treatment of hypertension as it produces quick relief to prolong relief from hypertension due to the effect of atorvastatin and atenolol respectively. Furthermore, prepared tablet showed comparable effect to marketed tablet.

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None

CONFLICT OF INTEREST

None

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