FORMULATION AND IN VITRO EVALUATION OF BILAYER TABLET OF ATENOLOL FOR BIPHASIC DRUG RELEASE

TARUN PARASHAR*, NARDEV SINGH

Department of Pharmaceutics, Uttaranchal Institute of Pharmaceutical Sciences, Dehradun, Uttarakhand, India.

Email: parashar89tarun@gmail.com

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ABSTRACT

Objective: In the present research work, the aim was to prepare the bilayer tablet of atenolol for biphasic drug release to improve its bioavailability and absorption in the lower gastrointestinal tract.

Methods: In the formulation of immediate release crospovidone, croscarmellose sodium, and sodium starch glycolate was used as super disintegrate and was directly compressed. For a sustained release portion different grade hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M, gum tragacanth, gum acacia, guar gum, and ethyl cellulose. Preformulation studies were performed before compression. The compressed bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time, and in vitro drug release using USP dissolution apparatus type 2 (paddle).

Results: The formulation IR3 showed 95% drug release in 30 min, and regression coefficient value ($r^2$) value was found to be 0.994 suggesting first-order drug release kinetics. The F9 formulation using HPMC K15M and gum acacia (1:1) showed 91.20% drug release at the end of 12 h, and regression coefficient value ($r^2$) was 0.992 suggesting zero-order drug release kinetics. Formulation IR3F9 showed faster drug release for bilayer tablet containing 5%w/w crospovidone in immediate release layer and HPMC and guar gum (1:1) in sustained release. Formulation IR3F9 showed swelling index 206%, floating lag time was found to be 2 min and total floating time up to 12 h.

Conclusion: The formulation IR3F9 showed a faster drug release profile among the others in the preparation of the atenolol bilayer tablet. Hence, it was considered as an optimized formulation.

Keyword: Bilayer tablet, Atenolol, Biphasic drug release, Swelling index.

INTRODUCTION

Oral drug delivery route is the most preferable route of drug delivery. It is due to the various advantages of this route such as ease of administration, patient compliance, and flexibility in the formulations. Oral absorption of drugs is often limited due to short gastric retention time. The gastric retention time is 3–4 h of human beings. The retention of drug delivery system in the stomach prolongs overall gastrointestinal (GI) transit time, thereby resulting in improved bioavailability. However, oral route has certain problems such as unpredictable gastric emptying rate, the short GI transit time and the existence of an absorption window in the gastric and upper small intestine for several drugs. The bilayer tablet effect of atenolol was always greater than the matrix tablet. Using immediate release dosage disintegrates rapidly and get dissolved to release the medicaments form the therapeutically effective concentration. For the preparation of biphasic release with variable concentrations of super disintegrant in immediate release layer and rate retarding polymer in sustained release layer for adjusting release pattern according to the need of therapy and IP guidelines of atenolol sustained release system. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as an initial dose and the second layer is maintenance dose. The present case 10 mg atenolol has to be released immediately, and the remaining 25 mg of atenolol has to be released in a sustained manner so that therapeutic concentration can be maintained. For the preparation of biphasic release with variable concentrations of super disintegrant in immediate release layer and rate retarding polymer in sustained release layer for adjusting release pattern according to the need of therapy and IP guidelines of atenolol sustained release tablet. In the bilayer tablet, one of the layers was formulated with super disintegrant for immediate drug release while another layer was formulated with the sustained release using a different polymer with a different ratio. The patient compliance when the drug has been used in a sustained release dosage form rather than conventional tablets and immediate release dosage form for the chronic patient of hypertension and angina pectoris [4-6].

MATERIALS AND METHODS

Materials

Atenolol was a gift sample from Elder Pharmaceutical Ltd., Dehradun. All ingredients used from college laboratory. All chemicals and reagents used were of analytical grade.
The atenolol immediate release layer was evaluated for angle of repose, precompression parameters of immediate release layer and sustained release layer for atenolol different formulations were made to achieve the desired drug release layers were identified on the basis of color since the immediate release die on SR layer and compressed using 9 mm circular punches. Both the amounts of the SR powder mixture were fed manually into the die cavity. In the present study, bilayer matrix tablet was prepared manually using the single station punching machine. Accurately weighed powder blend was passed through mesh size # 44. Then; binder preparation was added in the blended powder formation having a mesh size # 80. To mix the ingredients thoroughly drug and all the ingredients were accurately weighed and passed through sieve type).

Procedure for immediate release layer

All the ingredients were accurately weighed and passed through sieve having a mesh size # 80. To mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 min then; talc was mixed. After thoroughly mixing these ingredients, the powder blend was passed through mesh size # 44.

Procedure for sustained release layer

All the ingredients were accurately weighed and passed through sieve having a mesh size # 80. To mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 min then; binder preparation was added in the blended powder formation of the heap and passed through mesh size # 30 [7,8].

Compression of bilayer tablet

In the present study, bilayer tablet of 500 mg weight was prepared manually using the single station punching machine. Accurately weighed amounts of the SR powder mixture were fed manually into the die cavity. SR layer was compressed at mild compression force (2–3 kg/cm²) after that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 9 mm circular punches. Both the layers were identified on the basis of color since the immediate release layer had the pink color, and the sustained release layer has white color different formulations were made to achieve the desired drug release from the IR layer and SR layer of the bilayer tablet. The combination of the immediate release layer and sustained release layer for atenolol bilayer matrix tablets shown in Tables 1 and 2.

RESULTS

Precompression parameters of immediate release layer and sustained release layer [9,10]

The atenolol immediate release layer was evaluated for angle of repose, bulk density, tapped density, Hausner’s ratio (HR), and compressibility index. The bulk density was found in the range of 0.391–0.418 g/cm³. The tapped density was range 0.431–0.486 g/cm³. The angle of repose varied from 27.42° to 27.52°. The compressibility index was in the range of 12.43–15.20%. The HR was in the range of 1.152–1.172 shown in Table 3. The atenolol sustained release layer was prepared by the wet granulation method the powder was evaluated for angle of repose, bulk density, tapped density, HR, and compressibility index. The bulk density was found in the range of 0.202–0.486 g/cm³. The tapped density was range 0.192–0.556 g/cm³. The angle of repose varied from 27.20° to 31.40°. The compressibility index was in the range of 5.97–19.84%. The HR was in the range of 1.063–1.247 and the moisture content of the granules was range 0.43–0.67 % shown in Table 4.

Postcompression parameter of immediate release layer and sustained release layer [11,12]

The atenolol immediate release layer postcompression parameter was evaluated for hardness, friability, weight variation, thickness, and disintegration time. The hardness of tablet of each formulation was found in the range of 3.50±0.200–3.86±0.124 kg/cm². The friability was in the range of 0.20%–0.70%. The weight of each tablet formulation varied from 202±1.38 mg to 206±1.44 mg. All tablets were within the pharmacoepia limits of the weight. The weight of all tablets was found to be uniform with low standard deviation value. The thickness of all tablets was found in the range of 3.90±0.0054 mm–3.91±0.0050 mm. The disintegration time of all tablets was found in the range of 4.50 min–7.00 min parameter shown in Table 5. The atenolol sustained release layer postcompression parameter was evaluated for hardness, friability, weight, and thickness. The hardness of tablet of each formulation was found in the range of 4.55±0.165–7.12±0.139 kg/cm². The friability was range 0.2%–0.60%. The weight of tablet of each formulation in a tablet of each formulation varied from 301±1.48 mg to 309±1.38 mg all tablet was within the Indian Pharmacoepia limits of the weight. The weight of all tablets was found to be uniform with low standard deviation value. The thickness of all tablets was found in the range of 4.08±0.0039 mm–4.25±0.0045 mm. The drug content of all tablets was found in the range of 92.34±1.88%–98.50±1.22%. Swelling index and floating studies for sustained release were evaluated. The swelling index of tablet of each formulation was found in the range of 142.92–206.66%. The floating lag time was found in the range of 2 min–2.4 min. The floating time of all tablets was found 12 h. The percentage of yield was found in the range of 81–86% parameter shown in Table 6.

In vitro drug release study [13–17]

In vitro study was conducted using USP dissolution apparatus II (paddle type).

Dissolution profile for immediate release from IR1 was found (72% in 30 min) slower than IR2 and IR3. It has 5% w/w croscarmellose sodium used. IR2 formulation showed 84% drug release in 30 min. It

Table 1: Combination of immediate release layer for atenolol bilayer matrix tablets

| Formulation code | IR1 | IR2 | IR3 |
|------------------|-----|-----|-----|
| Atenolol         | 10  | 10  | 10  |
| MCC PH 102       | 90  | 90  | 90  |
| Lactose          | 84  | 84  | 84  |
| CCS              | 10  | -   | -   |
| SS               | -   | 10  | -   |
| Crospovidone     | 4   | 4   | 4   |
| Talc             | 2   | 2   | 2   |

Table 2: Combination of sustained release layer for atenolol bilayer matrix tablets

| Code      | F1   | F2   | F3   | F4   | F5   | F6   | F7   | F8   | F9   | F10  | F11  | F12  |
|-----------|------|------|------|------|------|------|------|------|------|------|------|------|
| Atenolol  | 25   | 25   | 25   | 25   | 25   | 25   | 25   | 25   | 25   | 25   | 25   | 25   |
| HPMC K4M  | 100  | 125  | 150  | 150  | 150  | 150  | 150  | 150  | 150  | 150  | 150  | 150  |
| HPMC K15M | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| Gum tragacanth | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| Rhyl cellulose  | 95   | 70   | 45   | 45   | 45   | 45   | 45   | 45   | 45   | 45   | 45   | 45   |
| Gum acacia     | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| Guar gum       | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| Sod.Bi-carbonate| 35   | 35   | 35   | 9    | 9    | 9    | 9    | 9    | 9    | 9    | 9    | 9    |
| Citric acid    | 20   | 20   | 20   | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| PVP k 30      | 19   | 19   | 19   | 30   | 30   | 30   | 30   | 30   | 30   | 30   | 30   | 30   |
| Mg. stearate   | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    |
| Talc          | 2    | 2    | 2    | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  |

HPMC: Hydroxypropyl methylcellulose
### Table 3: Micromeritic properties of precompression immediate release layer

| Code | Parameter          | Bulk density (g/cm³) | Tapped density (g/cm³) | Hauser’s ratio | Compressibility index (%) | Angle of repose |
|------|--------------------|----------------------|------------------------|----------------|---------------------------|-----------------|
| IR1  |                    | 0.391±0.02           | 0.461±0.01             | 1.152±0.02     | 12.43%±0.05               | 27.42±0.19     |
| IR2  |                    | 0.381±0.02           | 0.431±0.03             | 1.164±0.02     | 14.85%±0.13               | 27.52±0.16     |
| IR3  |                    | 0.418±0.01           | 0.486±0.01             | 1.172±0.01     | 15.20%±0.11               | 27.50±0.09     |

### Table 4: Micromeritic properties of precompression sustained release layer

| Code | Parameter          | Bulk density (g/cm³) | Tapped density (g/cm³) | Hauser’s ratio | Compressibility index (%) | Angle of repose | LOD % |
|------|--------------------|----------------------|------------------------|----------------|---------------------------|-----------------|-------|
| F1   |                    | 0.486                | 0.556                  | 1.219          | 12.589                    | 27.40°          | 0.43  |
| F2   |                    | 0.463                | 0.530                  | 1.144          | 12.641                    | 27.20°          | 0.54  |
| F3   |                    | 0.423                | 0.470                  | 1.111          | 10.00                     | 26.50°          | 0.65  |
| F4   |                    | 0.203                | 0.241                  | 1.187          | 15.76                     | 27.60°          | 0.53  |
| F5   |                    | 0.213                | 0.238                  | 1.117          | 10.054                    | 26.80°          | 0.55  |
| F6   |                    | 0.164                | 0.192                  | 1.170          | 14.55                     | 27.52°          | 0.51  |
| F7   |                    | 0.177                | 0.214                  | 1.120          | 17.28                     | 28.20°          | 0.54  |
| F8   |                    | 0.236                | 0.281                  | 1.190          | 16.014                    | 27.80°          | 0.54  |
| F9   |                    | 0.202                | 0.232                  | 1.148          | 12.931                    | 27.40°          | 0.56  |
| F10  |                    | 0.187                | 0.200                  | 1.069          | 6.50                      | 31.10°          | 0.55  |
| F11  |                    | 0.189                | 0.201                  | 1.063          | 5.97                      | 31.40°          | 0.65  |
| F12  |                    | 0.202                | 0.252                  | 1.247          | 19.84                     | 27.50°          | 0.67  |

### Table 5: Evaluation of atenolol immediate release layer

| Formulation code | Hardness (kg/cm²) | Friability (% w/w) | Weight variation (mg) | Thickness (mm) | Disintegration time (min) |
|------------------|-------------------|--------------------|-----------------------|----------------|--------------------------|
| IR1              | 3.50±0.200        | 0.70               | 206±1.44              | 3.90±0.0054    | 7.00                     |
| IR2              | 3.66±0.180        | 0.60               | 205±0.140             | 3.91±0.0050    | 6.30                     |
| IR3              | 3.86±0.124        | 0.20               | 202±0.138             | 3.91±0.0050    | 4.50                     |

### Table 6: Evaluation of atenolol sustained release layer

| Formulation code | Hardness (kg/cm²) | Friability (% w/w) | Weight Variation (mg) | Thickness (mm) | Drug Content (%) | Swelling index (%) | Floating lag time (min) | Floating time (h) | Percentage yield (%) |
|------------------|-------------------|--------------------|-----------------------|----------------|-----------------|-------------------|------------------------|-----------------|----------------------|
| F1               | 5.54              | 0.45               | 305                   | 4.10           | 95.20           | 146.43            | 2.0                    | 12              | 82                   |
| F2               | 5.52              | 0.50               | 301                   | 4.18           | 97.10           | 127.06            | 2.0                    | 12              | 84                   |
| F3               | 4.55              | 0.60               | 301                   | 4.20           | 95.23           | 179.66            | 2.0                    | 12              | 85                   |
| F4               | 6.60              | 0.25               | 303                   | 4.22           | 97.40           | 202.77            | 2.1                    | 12              | 86                   |
| F5               | 5.60              | 0.48               | 302                   | 4.25           | 95.67           | 155.70            | 2.5                    | 12              | 84                   |
| F6               | 6.58              | 0.27               | 308                   | 4.10           | 97.12           | 203.33            | 2.3                    | 12              | 81                   |
| F7               | 5.55              | 0.52               | 309                   | 4.10           | 94.30           | 142.92            | 2.2                    | 12              | 83                   |
| F8               | 4.62              | 0.58               | 308                   | 4.14           | 92.42           | 168.65            | 2.4                    | 12              | 82                   |
| F9               | 6.61              | 0.30               | 309                   | 4.08           | 98.75           | 206.00            | 2.2                    | 12              | 86                   |
| F10              | 6.66              | 0.25               | 306                   | 4.17           | 92.34           | 192.43            | 2.3                    | 12              | 81                   |
| F11              | 6.63              | 0.25               | 307                   | 4.11           | 93.14           | 181.67            | 2.2                    | 12              | 83                   |
| F12              | 7.13              | 0.20               | 308                   | 4.08           | 98.50           | 206.66            | 2.0                    | 12              | 85                   |

HPMC: Hydroxypropyl methylcellulose

### Table 7: Dissolution drug profile of Bilayer formulations

| Sl. No. | Time (min) | Cumulative percentage drug release (IR3 F4) | Cumulative percentage drug release (IR3 F6) | Cumulative percentage drug release (IR3 F9) | Cumulative percentage drug release (IR3 F12) |
|---------|------------|-------------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------------|
| 1       | 15         | 30.23                                     | 28.56                                    | 26.62                                    | 32.46                                     |
| 2       | 30         | 45.67                                     | 47.32                                    | 43.46                                    | 45.25                                     |
| 3       | 60         | 52.58                                     | 55.82                                    | 54.21                                    | 57.48                                     |
| 4       | 120        | 59.80                                     | 62.81                                    | 60.38                                    | 66.56                                     |
| 5       | 240        | 68.29                                     | 70.48                                    | 66.34                                    | 75.43                                     |
| 6       | 480        | 76.98                                     | 78.34                                    | 72.84                                    | 83.71                                     |
| 7       | 960        | 90.12                                     | 91.11                                    | 95.23                                    | 92.81                                     |

HPC: Hydroxypropyl cellulose
has 5% w/w sodium starch glycolate used. IR3 formulation showed 95% drug release in 30 min, and regression coefficient value ($r^2$) value was found to be 0.994. It has 5% w/w crospovidone used comparative in vitro drug release pattern of immediate release layers. The formulation IR3 showed best cumulative drug release. All formulations of immediate release support the first-order kinetics. Therefore, IR3 was selected for further studies.

Dissolution profile for sustained release F1 to F12 formulation cumulative drug determine release was up to 12 hrs. The F1, F2, and F3 formulation showed 81.98%, 83.97%, and 78.29%; cumulative drug release using hydroxypropyl methylcellulose (HPMC) K4M and ethyl cellulose. The F4, F5, and F6 formulation showed 92.46%, 79.38%, and 92.72%; cumulative drug release using HPMC K15M and gum tragacanth. The formulation F7, F8, and F9 formulations showed 74.14%, 83.28%, and 91.20%; cumulative drug release using HPMC K15M and gum acacia. The formulation F10, F11, and F12 formulation showed 72.67%, 69.19%, and 93.65%; cumulative drug release using HPMC K15M and guar gum. The formulation F4, F6, F9, and F12 showed best cumulative drug release. Therefore F4, F6, F9, and F12 were selected for further studies.

Dissolution profile for bilayer tablet IR3F4, IR3F6, IR3F9, and IR3F12 formulation cumulative drug release showed 90.12%, 91.11%, 95.23%, and 92.81% shown in Table 7 and Fig. 1. The formulation cumulative drug release was found up to 12 h. Therefore, IR3F9 was found to be the best formulation among all of them because of its good relationship between cumulative percentage drug releases and time was 95.23% up to 12 h.

Kinetic release modeling [18-21]
The release profiles of an immediate release layer of all formulations were compared with zero-order, the first-order model. The data were processed for regression analysis using MS-Excel statistical functions. The data were evaluated for zero-order, the first-order model, the IR1 to IR3 values obtained were shown in Table 8. The formulation IR3 showed regression coefficient value ($r^2$) is 0.994. The data suggested that release kinetics follow first-order drug release because the values of regression coefficient obtained for first-order release profiles are near to 1 as compared to zero-order.

The release profiles of a sustained release layer of all formulations were compared with zero-order, first-order, Higuchi model, and Korsmeyers–Peppas model value shown in Table 9. The cumulative percentage drug release F4, F6, F9, and F12 was higher than other formulation shown in Table 10, Figs. 2 and 3 and regression coefficient value ($r^2$) 0.968, 0.986,

### Table 8: Kinetic data of immediate release

| Formulation code | Zero-order | First-order | Best fit model |
|------------------|------------|-------------|----------------|
|                  | $R^2$      | $R^2$       |                |
| IR1              | 0.963      | 0.986       | First order    |
| IR2              | 0.957      | 0.993       | First order    |
| IR3              | 0.930      | 0.994       | First order    |

Fig. 1: Cumulative percent drug released versus time plots of formulations IR3 F4, IR3 F6, IR3 F9, and IR3 F12

Fig. 2: Cumulative percent drug released versus time plots of formulations IR3 F4, IR3 F6, IR3 F9, and IR3 F12

Fig. 3: Release kinetics of optimized formulation IR3F9
Table 9: Kinetic data of sustained release

| Formulation code | Zero-order R² | First-order R² | Higuchi R² | Peppas R² | n | Best fit model |
|------------------|---------------|---------------|------------|------------|---|----------------|
| F1               | 0.875         | 0.970         | 0.980      | 0.979      | 0.512 | Higuchi        |
| F2               | 0.850         | 0.982         | 0.980      | 0.943      | 0.485 | First          |
| F3               | 0.885         | 0.941         | 0.967      | 0.942      | 0.700 | Higuchi        |
| F4               | 0.850         | 0.980         | 0.975      | 0.970      | 0.454 | First          |
| F5               | 0.885         | 0.970         | 0.972      | 0.962      | 0.671 | Higuchi        |
| F6               | 0.986         | 0.970         | 0.920      | 0.975      | 0.590 | Zero           |
| F7               | 0.857         | 0.941         | 0.965      | 0.952      | 0.623 | Higuchi        |
| F8               | 0.874         | 0.968         | 0.966      | 0.952      | 0.642 | First          |
| F9               | 0.992         | 0.905         | 0.986      | 0.979      | 0.570 | Zero           |
| F10              | 0.932         | 0.980         | 0.967      | 0.964      | 0.531 | First          |
| F11              | 0.944         | 0.979         | 0.985      | 0.962      | 0.712 | Higuchi        |
| F12              | 0.990         | 0.944         | 0.972      | 0.967      | 0.531 | Zero           |

Table 10: In vitro drug release data of bilayer formulations

| Time (min) | Cumulative percentage drug release (IR3 F4) | Cumulative percentage drug release (IR3 F6) | Cumulative percentage drug release (IR3 F9) | Cumulative percentage drug release (IR3 F12) |
|------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
| 15         | 30.23                                     | 28.56                                     | 26.62                                     | 32.46                                     |
| 30         | 45.67                                     | 47.32                                     | 43.46                                     | 45.25                                     |
| 60         | 52.58                                     | 55.82                                     | 54.21                                     | 57.48                                     |
| 120        | 59.80                                     | 62.81                                     | 60.38                                     | 66.56                                     |
| 240        | 68.29                                     | 70.48                                     | 66.34                                     | 75.43                                     |
| 480        | 76.98                                     | 78.34                                     | 72.84                                     | 83.71                                     |
| 960        | 90.12                                     | 91.11                                     | 95.23                                     | 92.81                                     |

0.992, and 0.944. Moreover, these formulations support the ‘n’ value is in the range 0.45–0.60 also having higher percentage cumulative drug release. After evaluating above parameters, these four formulations were selected for further study.

DISCUSSION

The drug atenolol was selected for the study because it is nicely fitted in the designed formula and its low bioavailability. Melting point and IR spectra identification results of drug indicate the purity of the drug. IR spectra of pure drug and with the excipients are identical and do not show any incompatibility; thus the excipients are compatible with the drug. Formulation IR3F9 showed flow properties of powder blends. The value of the angle of repose was found to be 27.50°, HR was found to be 1.172, and compressibility index was found to be 15.20%. The value of angle of repose was found to be 27.40°, HR 1.148, and compressibility index was found to be 12.93% indicate good flow properties of powder blends. Friability and hardness were within the pharmacopeial limits thus showing the good mechanical strength of tablets. Formulation IR3F9 showed the drug release for tablet faster release, which contains 5% w/w crospovidone in immediate release layer and sustained release which containing HPMC and guar gum (1:1). Formulation IR3F9 showed the swelling index was found to be 206%, floating lag time was found to be 2 min and total floating time up to 12 h. Dissolution profile for bilayer tablet IR3F9 formulation a good relation between cumulative drug release and time. The release pattern showed 95.23% up to 12 h.

CONCLUSION

Atenolol is a β-adrenoceptor antagonist or more commonly known as a beta-blocker. It is incompletely absorbed from the GI tract. Bilayer tablet formulation is containing the immediate release and sustained release. In which one layer is formulated to obtain the immediate release of the drug; with the aim of reaching a high serum concentration in a short period of time and the second layer is a controlled release hydrophilic matrix; which is designed to maintain an effective plasma concentration of the drug in the blood for a prolonged period of time which help to decrease the frequency of dosing and also improve the efficacy of drug and patient compliance. Hence, an attempt was made to formulate a bilayer tablet of the antihypertensive drug to diagnose and cure hypertension and angina pectoris for chronic patients.

CONFLICTS OF INTERESTS

None.

AUTHORS CONTRIBUTION

Tarun Parashar-Designed the study, developed the methodology, collected the data and performed the analysis and wrote the manuscript. Nardev Singh-contributed in writing the manuscript.

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