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Short communication

Stability of amlodipine besylate and atenolol in multi-component tablets of mono-layer and bi-layer types

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Multi-drug tablets of amlodipine besylate and atenolol were prepared as either mono-layer (mixed matrix) or bi-layer tablets containing each drug in a separate layer by using similar excipients and processing. Each tablet batch was packed in strip and blister packs and kept under accelerated temperature and humidity conditions. The stability of two tablet and packaging types was compared by HPLC analysis after 0, 1, 3 and 4.5 months and expressed as the content of intact amlodipine and atenolol. The content of atenolol did not decline regardless of tablet and packaging type. Amlodipine content in bi-layer tablets decreased to about 95 and 88% when packed in strips and blisters, respectively. When prepared as mono-layer tablets, the content decreased to 72 and 32%, respectively.

The study revealed that the bi-layer tablet formulation was more stable than the mono-layer type. Further, the stability was increased when the tablets were packed in aluminium strips as compared to PVC blisters.

Keywords: amlodipine, atenolol, mono-layer, bi-layer tablet, stability

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Fixed-dose drug combination decreases the risk of patient non-compliance and should be considered in patients with chronic conditions like hypertension (1). Clinically, combination therapy in hypertension treatment involving two or more drugs from different classes can result in better drug efficacy and is recommended for the initial stage of hypertension treatment (2). The combination of atenolol and amlodipine significantly decreases blood pressure and systolic blood pressure variability. In spontaneously hypertensive rats, the synergistic effect between atenolol and amlodipine results in lowering and stabilizing of blood pressure (3). Both beta blockers and dihydropyridine calcium antagonist are widely used in the treatment of hypertension. Their combination is a logical choice and can also neutralize the side effects of each drug. Combination therapy is likely to be the optimal way to control blood pressure and reduce blood pressure

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variability in the treatment of hypertension as well as in prevention of stroke in hypertension (4). The stability of the product, on the other hand, remains a pharmaceutical challenge in multi-drug formulations.

Amlodipine besylate, like all members of 1,4-dihydropyridine calcium channel blockers, is photosensitive and liable to degradation both in solution and in solid state. Light catalyses its oxidation to pyridine derivatives, such as amlox (2-[(2-aminoethoxy)met - hyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl pyridine), which lack therapeutic effects (5). Forced degradation studies show amlodipine to be degrading slowly under thermal stress (more in solution than in solid state), degrading faster under photo-stress (more rapidly under UV 366 nm than under 254 nm and less in natural light) and even more under acidic, alkaline and oxidative stress – the highest being in alkaline conditions (6, 7). Another pharmaceutical problem is the reported incompatibility in the solid formulation between amlodipine besylate and lactose in the presence of basic excipients (magnesium stearate) and water (8). Atenolol is reported to be photoreactive when exposed to UVA–UVB radiation with photodegradation increasing with a decrease in the pH value. The main photodegradation product at pH 7.4 was identified as 2-(4-hydroxyphenyl) acetamide (9).

This research work was designed to compare the stability of two types of tablets – a mono-layer tablet containing amlodipine besylate and atenolol in the same matrix and a bi-layer tablet containing amlodipine besylate and atenolol in separate layers. Similar excipients, processing and storage conditions were applied for both tablet types and two different packaging materials (aluminium and PVC) were used to study the influence of packaging material. The results were obtained from HPLC analyses of drug content in the tablets stored under accelerated temperature and humidity conditions.

EXPERIMENTAL

Materials

All the materials were generously provided by Quest Pharmaceuticals (P) Ltd, Nepal. All raw materials used to manufacture the tablets were of pharmaceutical grade and included amlodipine besylate BP (Cadila Pharma, India), atenolol IP (IPCA Laboratories, India), maize starch IP (Universal Starch, India), microcrystalline cellulose (powder) IP (Chemsfield, India), calcium hydrogen phosphate dihydrate IP (Enar Chemie, India), sodium starch glycolate IP (Universal Starch, India), magnesium stearate IP (Paras Fine Organics, India), colloidal silicon dioxide IP (Degussa, Belgium) and erythrosine lake colour ISI (Roha Dye Chem, India).

Chemicals and solvents for analysis: methanol, acetonitrile and water for HPLC (LiChrosolv brand) were purchased from Merck Ltd, India. Triethylamine was a product of Qualigens Fine Chemicals, India. Sodium octane sulphonate (1-octane sulphonic acid sodium salt) for chromatography was purchased from Spectrochem, India, and *o*-phosphoric acid, from Central Drug House, India. All the chemicals used were of analytical grade.

Working standards of amlodipine besylate and atenolol were also kind gifts from Quest Pharmaceuticals (P).

Manufacturing and packaging of tablets

Both types of tablets were manufactured in batches of ten thousand tablets each as per formulae given in Table I. Three granulations were prepared separately – two single ingredient granules of amlodipine and atenolol and one of mixed granules containing both. All the granules were prepared by the wet granulation method using starch paste as a binder. The active ingredients and colour (in amlodipine granules) were mixed with the diluents using the geometrical dilution method manually and granulated by mixing

Table I. Mono-layer (A) and bi-layer tablet formulations (B)

A	mg per tablet
Amlodipine besylate	6.90
Atenolol	50.00
Maize starch	90.10
Microcrystalline cellulose (powder)	95.00
Calcium hydrogen phosphate dihydrate	90.00
Sodium starch glycolate	15.00
Magnesium stearate	1.00
Colloidal silicon dioxide	2.00
Total mass of mono-layer tablet	350.00
B. *Amlodipine layer*	
Amlodipine besylate	6.90
Maize starch	50.10
Microcrystalline cellulose (powder)	50.00
Calcium hydrogen phosphate dihydrate	40.00
Sodium starch glycolate	15.00
Magnesium stearate	1.00
Colloidal silicon dioxide	2.00
Erythrosine Lake colour	0.15
Total mass	165.00
B. *Atenolol layer*	
Atenolol	50.00
Maize starch	50.00
Microcrystalline cellulose (powder)	40.00
Calcium hydrogen phosphate dihydrate	32.00
Sodium starch glycolate	10.00
Magnesium stearate	1.00
Colloidal silicon dioxide	2.00
Total mass	185.00
Total mass of bi-layered tablet	350.00

with starch paste in a paddle type Mass Mixer (10 liter capacity, Grovers Equipments, India). The wet mass were shredded from a 16 mesh sieve and dried in a fluidized bed dryer (30 kg capacity, Kothari Pharma, India) at 50 °C until the moisture content (determined by a moisture balance, IR-30 Denver Instruments, USA) came to about 4.5%. Finally, the granules were sieved again from a 16 mesh sieve (1.19 mm), mixed with sodium starch glycolate and lubricated with magnesium stearate and colloidal silicon dioxide as per their respective formulae.

The lubricated granules were compressed into mono-layer and bi-layer tablets using a 27-station double-sided Rotary Tablet Press (Cadmach, India). A set of round biconvex 10-mm diameter punches was used for both tablet types. Mono-layer tablets were compressed at a theoretical average mass of 350 mg. Bi-layer parts were used to compress amlodipine (pink) and atenolol (white) as separate layers in the bi-layer tablet. The mass of amlodipine layer was adjusted to 165 mg and atenolol layer to 185 mg, making the final tablet mass 350 mg. Vacuum was employed in the suction port of the machine to avoid mixing of the two granules.

Both types of tablets were then packed in strips and blisters of 10 tablets each. Strips were prepared from 0.03 mm polylaminated aluminium foils (Hindalco, India) using a strip packing machine (Kulbindra Engineering, India). Blisters were packed in 0.025 mm heat sealing laquer (HSL)-coated aluminium foil (Hindalco, India) and 0.25 mm clear transparent PVC (Fenoplast India) using a blister machine (Elmach Packaging, India).

Assay of amlodipine and atenolol

Instrumentation. – Isocratic HPLC System (Knauer, Germany) was used for the analysis. The solvent delivery system consisted of a Smartline HPLC pump model 1000 with a 10-mL pump head. The detector was a spectrophotometer type Smartline UV 2500. PC-based software Eurochrom 2000 for Windows, V.3.05, was employed for data acquisition, processing and instrument control. A 20-μL loop was used for sample injection. Reversed phase octadecyl silane (ODS) C-18 column stainless steel, 250 mm x 4.6 mm internal diameter, with 10 μm particle size (Eurosper 100-10, Knaur) was used as the analytical column. The analysis was carried out at a 1.5 mL min^{-1} flow rate and detection at 238 nm. Analytical columns were used at ambient laboratory temperature that was kept within 22–27 °C with a room air conditioner.

Mobile phase preparation. – Mobile phase consisted of HPLC grade water/methanol/acetonitrile (34:33:33) containing triethylamine (0.034%) and sodium octane sulphonate (0.1%). The pH of the solution was adjusted to 2.8 with 50% *o*-phosphoric acid. The solution was sonicated for 5 min with a laboratory sonicator (6 l model, Medica Instruments, India) and filtered from Axiva brand disc filters (0.45 μm; Axiva Sichem (P) Ltd, India) using a vacuum filtration kit.

Standard preparation. – Amlodipine besylate accurately weighed to 69.00 mg (equivalent to 50.00 mg amlodipine) was transferred to a 50-mL volumetric flask and dissolved in about 25 mL of mobile phase by manual shaking and the volume was adjusted with the mobile phase. An liquot (5 mL) of the above solution was transferred to a 100-mL volumetric flask. Atenolol (50.00 mg) was dissolved in about 50 mL of mobile phase by manual shaking and the final volume (100.00 mL) was adjusted with the mobile phase.

The solution was finally filtered using a syringe filtration kit from Ultipore (N66 brand 0.2 μm membrane filter, 13 mm diameter; PALL Life Sciences, India).

Sample preparation. – Sample tablets were removed from their strip/blister and the average mass of 20 tablets was determined. The tablets were crushed using a mortar and pestle to fine powder. A quantity of powder equivalent to the average mass of the tablets was accurately weighed and transferred to a 100-mL volumetric flask. The flask was half-filled with the mobile phase and shaken manually for 10 minutes. The volume was made up to 100 mL with the mobile phase and kept in the sonicator for 10 minutes. An aliquot of the solution was centrifuged for 5 min at 2500 rpm; about 2 mL of the solution was then filtered through a 0.2 μm Ultipore N66 membrane filter and kept in the sample vial with an air tight lid.

Stability study. – The samples were kept in the stability chamber (Thermaolab, India) set at accelerated storage conditions (10) of 40 ± 2 °C and 75 ± 5% relative humidity. Contents of both amlodipine and atenolol in the samples were periodically monitored by the HPLC analysis. Analyses were carried out at time 0 and after storage of 1, 2, 3, and 4.5 months in the stability chamber. The comparison was statistically evaluated by Student's *t* test.

RESULTS AND DISCUSSION

Amlodipine and atenolol combined in the same drug dosage form are gaining popularity among pharmaceutical manufacturers. However, data on the stability of such products are not disclosed and remain mostly with the manufacturer. As the combination of amlodipine and atenolol is not official in the therapeutic Compendia, quantitative analyses of amlodipine (6, 11, 12) and atenolol (13, 14) in pharmaceutical dosage forms are generally described by UV spectrophotometric and high performance liquid chromatographic techniques. Determination of both components in multi-drug tablets is done by various methods such as UV spectrophotometry, HPLC, and HPTLC (15, 16).

Resolution of multicomponent preparations is often a complex analytical problem since combined substances may have different chemical structures but similar properties, *e.g.*, chromatographic behaviour (13). Therefore, the development and validation of the modified analytical method for the concomitant assay of amlodipine and atenolol consumed considerable time of the research. The methods described in the literature for the determination of amlodipine and atenolol (11, 12, 15, 16) were, in our conditions, found to be unsuitable regarding the resolution of components, large tailing factors and inconsistency. We based our method on the conditions described by Klinkenberg *et al.* (11) but we had to adjust the mobile phase composition. The analytical variables were optimized to obtain the desired chromatographic characteristics, including resolution of the components, peak symmetry (tailing factors at least less than 2) and theoretical plate numbers over 1000 (10).

Validation of the HPLC method

As we adjusted the assay conditions, validation of the modified method was necessary. The method was validated through injection repeatability, linearity tests, recovery

test, *LOD*, *LOQ*, and accuracy (11). In the injection repeatability test, the relative standard deviations (RSD) of the peak area of six consecutive injections were found to be 0.8 and 0.7% for atenolol and amlodipine, respectively. Linearity test for the response was conducted by using five standard solutions containing 40, 45, 50, 55, and 60 μg mL^{-1} of amlodipine base and 400, 450, 500, 550, and 600 μg mL^{-1} of atenolol, respectively. Regression analysis showed satisfactory results with the squared value of the Pearson product moment correlation coefficient of 0.9966 for amlodipine and 0.9989 for atenolol. The recovery test (in triplicate, the standard addition method) was carried out using simulated tablet samples (samples of a known quantity of the drug along with placebo mixtures of excipients in the same composition as in the actual mono-layer tablets) of 90, 100 and 110% strength. The test resulted in mean recovery of 99.8% ± for amlodipine and 99.5% ± for atenolol and showed acceptable accuracy. The mean recovery was in good agreement with the published data for amlodipine (12) and atenolol (13, 14). Limit of detection (*LOD*) was found to be 3.63 and 5.31 μg mL^{-1} for amlodipine and atenolol, respectively. Limit of quantification (*LOQ*) was 11.01 and 16.09 μg mL^{-1} for amlodipine and atenolol, respectively. The values for *LOD* and *LOQ* were rather high compared to the values of Klinkenberg *et al.* (11), who were determining the residues of amlodipine alone, whereas, we were dealing with a mixed drug system.

Specificity tests were carried out by comparing the chromatographic peaks of the mobile phase only, excipients (placebo mixture) added to the mobile phase and treated like the sample and the standard containing amlodipine and atenolol. Placebo mixture was prepared by mixing the same excipients in the same composition as in the actual mono-layer tablets. Placebo was added to standard solutions in the same proportion that would be contained in the dilution of the actual formulation. The chromatogram with only placebo showed no significant peaks in the positions where the principal peaks would appear (Fig. 1). The chromatographic results of the standard with and without addition of the excipients were compared and no changes were observed after addition of excipients. It is known that atenolol can be determined in the presence of its major degradation product (14) and therefore the measurements were focused on drugs content alone.

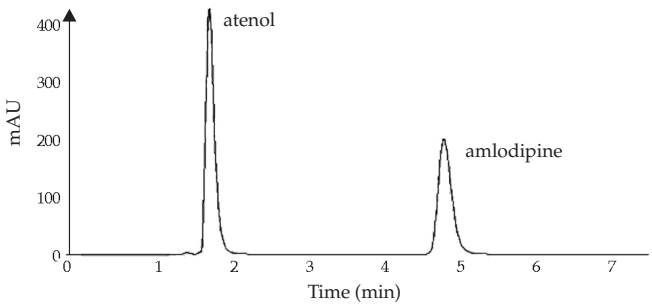

Fig. 1. A representative chromatogram and the chromatographic parameters of a standard solution containing amlodipine (t_R = 4.95 ± 0.11 min) and atenolol (t_R = 1.85 ± 0.01 min). HPLC conditions: column: RP_{18} (ODS, 4.6 x 250 mm); eluent: water/methanol/acetonitrile (34:33:33) with triethylamine (0.034%) and sodium octane sulphonate (0.1%), pH 2.8; flow rate: 1.5 mL min^{-1}; detection: UV 238 nm.

Table II. Accelerated stability tests[a,b]

Time (month)	Strip packs				Blister packs			
	Amlodipine		Atenolol		Amlodipine		Atenolol	
	Mono-layer tablet	Bi-layer tablet	Mono-layer tablet	Bi-layer tablet	Mono-layer tablet	Bi-layer tablet	Mono-layer tablet	Bi-layer tablet
0	97.5 ± 0.7	100.3 ± 1.0	99.3 ± 0.8	97.5 ± 0.9	97.5 ± 0.7	100.3 ± 1.0	99.3 ± 0.8	97.5 ± 0.9
1	84.8 ± 0.7[b]	102.2 ± 0.6	97.1 ± 1.1	97.3 ± 0.2	88.4 ± 0.1[a]	97.7 ± 0.1	102.0 ± 0.3	97.7 ± 0.3
3	75.8 ± 0.1[b]	97.1 ± 0.5	99.9 ± 0.3	98.7 ± 0.3	44.5 ± 0.4[b]	91.5 ± 0.3[a]	100.7 ± 0.2	95.5 ± 0.2
4.5	72.2 ± 0.1[b]	95.5 ± 0.5[b]	99.4 ± 0.3	98.5 ± 0.0	32.2 ± 0.0[b]	88.0 ± 0.3[a]	101.9 ± 1.4	100.3 ± 0.2

[a] The conditions were: 40 ± 2 °C and 70 ± 5% relative humidity.
[b] All values (from two separate experiments with triplicate measurements) represent the percentage of the labeled amount ± SD.
Statistical significance by Student's *t* test ([a] $p < 0.05$, [b] $p < 0.005$) as compared to the values at time 0.

Stability tests

The stability test results in terms of the average content of amlodipine and atenolol per tablet, in percentage with respect to the labeled amount, are presented in Table II. The quantity of atenolol remained fairly constant in both strip and blister packing until the end of the stability study period (4.5 months). No significant degradation was observed in either the mono-layer or bi-layer tablets (Table II).

Amlodipine content in the strip packaging decreased, in the mono-layer tablets, to 72.2% ($p < 0.005$). When prepared as bi-layer tablets and packed in strips, a significant decrease ($p < 0.005$) was observed only after 4.5 months of storage. To be sure that the values were the result of degradation and not of variability in tablet mass, we determined the tablet mass variation for the mono-layer type (+2.2 and –1.7%) and the bi-layer type (+2.3 and –3.1 %). Moreover, we also determined the individual mass variations in separate layers and found them to be +4.3 and –3.7% for the atenolol layer and +3.8 and –6.2% for the amlodipine layer. Taking into account individual mass variations, the decrease in the amlodipine content in bi-layer tablets packed in strips does not represent a significant degradation. Amlodipine content sharply decreased in the blister packed tablets – both in the mono-layer ($p < 0.005$) and bi-layer formulations. The decrease was more dramatic in the mono-layer type dropping to about 32.3% within 4.5 months (Table II). This significant decline in content ($p < 0.005$) is clearly the result of amlodipine degradation since it is more than what could be contributed to mass variation.

The stability results suggest that atenolol was fairly stable in both formulations in strip packing (Table II). The variations in atenolol content (from 97.1 to 102.0%) correspond to the tablet mass variation +4.3 to –3.7%. The contribution from tablet mass variation can be expected to be a little higher in bi-layer tablets than in mono-layer tablets. On the other hand, the content of amlodipine in mono-layer strips, mono-layer and bi-layer blisters was gradually decreasing with a significant change (more than 5%) as per ICH (10). The results (Table II) indicate that, in regard to amlodipine content, strip packaging is preferable to blister packaging ($p < 0.005$). Moreover, the bi-layer type is significantly ($p < 0.005$) more suitable than the mono-layer type for all combined type formulations. Although the manufacturing of bi-layer tablets requires more time, skill and financial resources, it appears to be a preferable choice for combined drugs formulations.

As no literature data are available on the stability of the combination dosage forms of these two drugs, we expect that more research will be done into the stability problems of such combined formulations.

CONCLUSIONS

Amlodipine degraded more rapidly than atenolol in both types of tablets and packing materials. The drugs in bi-layered tablets were found to be more stable than in mono-layer tablets, and strip packaging was found to be superior to blister packaging considering the stability parameter. We recommend the bi-layered type tablets packed in aluminium strips as a preferable choice for formulation of amlodipine and atenolol as single dosage form tablets. It would be interesting to confirm the degradation products of both drugs, and to quantify them.

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S A Ž E T A K

Stabilnost amlodipin besilata i atenola u jednoslojnim i dvoslojnim tabletama

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Tablete s amlodipinom i atenololom pripremljene su ili u obliku jednoslojne tablete (miješani matriks) ili kao dvoslojne tablete (lijekovi u zasebnim slojevima) koristeći slične pomoćne tvari i uvjete tabletiranja. Tablete su pakirane u dvije vrste pakiranja, aluminijske folije (strip) ili PVC (blister) i čuvane u uvjetima ubrzanog starenja. Stabilnost je određivana pomoću HPLC metode nakon 0, 1, 2, 3 i 4,5 mjeseci i izražena kao sadržaj intaktnog lijeka.

Sadržaj atenolola nije se značajno promijenio bez obzira na tip tablete ili pakiranje. Sadržaj amlodipina u dvoslojnim tabletama smanjio se na 95% (tablete u strip pakiranju) i 88% (tablete u blister pakiranju). Istodobno, u jednoslojnom tipu kombiniranih tableta sadržaj se smanjio na 72% (strip pakiranje) i 32% (blister pakiranje).

Rezultati pokazuju da su dvoslojne tablete s amlodipinom i atenololom stabilnije od jednoslojnih. Štoviše, pakiranje tableta u aluminijsku foliju u obliku strip pakiranja povećava njihovu stabilnost u usporedbi s PVC pakirnim materijalom (blister).

Ključne riječi: amlodipin, atenolol, jednoslojna, dvoslojna tableta, stabilnost

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