Bilayer Tablets of Atorvastatin Calcium and Nicotinic Acid: Formulation and Evaluation

Jayabalan NIRMAL,*[,a] Srinivasan SAISIVAM,[b] Chintalapati PEDDANNA,[b] Selvadurai MURALIDHARAN,[c] Sundaram GODWINKUMAR,[b] and Muthuraja NAGARAJAN[b]

[a] *Department of Pharmaceutics, K.M. College of Pharmacy; Madurai 625107, Tamil Nadu, India:* [b] *Microlabs; Hosur 635126, Tamil Nadu, India: and* [c] *Department of Pharmaceutical Analysis, J.S.S. College of Pharmacy; Ootacamund 643001, Tamil Nadu, India.* Received February 5, 2008; accepted May 19, 2008; published online August 8, 2008

The objective of the study is to formulate bilayer tablets consisting of atorvastatin calcium (AT) as an immediate release layer and nicotinic acid (NA) as an extended release layer. The immediate release layer was prepared using super disintegrant croscarmellose sodium and extended release layer using hydroxypropylmethyl cellulose (HPMC K100M). Both the matrix and bilayer tablets were evaluated for hardness, friability, weight variation, thickness, and drug content uniformity and subjected to *in vitro* drug release studies. The amount of AT and NA released at different time intervals were estimated by HPLC method. The bilayer tablets showed no significant change either in physical appearance, drug content or in dissolution pattern after storing at 40 °C/75% relative humiding (RH) for 3 months. The release of the drug from the tablet was influenced by the polymer content and it was much evident from thermogravimetry/differential thermal analysis (TG/DTA) analysis. The results indicated that the bilayer tablets could be a potential dosage form for delivering AT and NA.

Key words bilayer tablet; atorvastatin calcium; nicotinic acid

For many years, oral drug delivery continues to be the preferred route of pharmaceutical administration of many drug substances.[1,2] Approaches and technologies in the area of modified release oral drug delivery have been developed to extend the release of drug over a number of hours, an effect accomplished either by combining the drug with release retardant materials to form a matrix core, or applying release modifying film coatings to cores containing the drug.[3] For developing matrix tablet, various materials like waxes, hydrophilic and hydrophobic polymers and gums have been employed in the formulation.[4] Among these polymers, the use of hydrophilic matrices has been extremely popular in controlling the release of drug from solid dosage forms.[5—9] Among the hydrophilic polymers, swellable and hydrophilic property of hydroxypropylmethyl cellulase (HPMC) has been paid considerable attention for the preparation of matrix tablets as sustained release formulation of various drugs.[10,11] Further, various research on HPMC has been studied and reported by several research groups.[12—14]

In the pharmaceutical dosage forms several approaches are available to include the loading dose of a drug to the maintenance dose of a drug for sustained action. A novel approach for having the loading dose and maintenance dose in a tablet is the formulation of drugs in a multilayered/bilayer tablet.[15] By using multilayer or bilayer tablet system, it makes possible to design extended release preparations with an immediate release quantity in one layer and an extended release portion in the second, thus maintaining a prolonged blood level. The immediate release portion will disintegrate rapidly after ingestion, thus providing the initial dose of medication for immediate onset of action where as the matrix layer remain intact during most of the time of its passage through the intestine, while dissolving slowly from its exposed faces in this passage, which helps to maintain the blood level that initially reached.[16,17] Similarly, one drug can be administered for immediate release and another drug can be for sustained release.[18,19]

The purpose of this study was to formulate bilayer tablets of atorvastatin calcium (AT) as an immediate release layer and nicotinic acid (NA) as an extended release layer. Both drugs having different mechanism of action were combined to achieve the same goal. The combination of these two drugs shows a significant reduction in low density lipoprotein cholesterol with favorable changes in high density lipoprotein cholesterol, lipoprotein and triglycerides. Compared to other types of formulation of NA, extended release form has fewer side effects.[20,21] The selected drug NA is a water soluble drug and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug.[22] In this study HPMC K100M was used as polymeric carrier for NA to investigate the drug release behaviour for 12 h.

Experimental

Atorvastatin calcium and nicotinic acid were purchased from Cadila Health Care Ltd., India. Microcrystalline cellulose powder (MCC; Avicel PH 101) and MCC Ranq (Avicel PH 112) (Gufic Biosciences, India), polyvinylpyrrolidone (BASF, Germany), hydroxypropylmethyl cellulose; HPMC K100M (Vigro Chem, India), Colloidal silicon dioxide (Degussa, W. Germany) and Croscarmellose sodium (Hetero Drugs, India) were purchased from the suppliers mentioned in the parentheses. Other chemicals and solvents used were of Analaytical grade.

Preformulation Studies The physical parameters like angle of repose, loss on drying, bulk and tap densities, Carr index and Hausner ratio were determined for AT and NA.[23—26]

Compatibility Study About 11.8 mg of AT and 375 mg of NA alone and the physical mixtures consisting of AT with various excipients and NA with various excipients in 1 : 1 and 1 : 10 ratio in a glass vial were taken and kept at various stability conditions (30 °C/65% RH, 40 °C/75% RH and 60 °C/80% RH) in stability chamber (Newtronic Walk-in Humidity chamber, India) for 1 month in open and closed condition. The samples were withdrawn and checked for colour change, if any on day 1, 2, 3, 4, 5, 6, 7, 14, 21 and 30. Finally, the combination of mixtures without colour changes was selected for tablet formulation.

Preparation of HPMC Matrix for NA Layer Matrix tablet was prepared by aqueous and non-aqueous granulation method. The required materials (Table 1) were passed through # 40 sieve. All materials except polyvinyl pyrrolidone (PVP) and lubricants were thoroughly mixed in a polybag for 30 min and then granulated using PVP as a binder solution. The wet gran-

* To whom correspondence should be addressed. e-mail: nirmal21pharm@rediffmail.com

Table 1. Composition of Nicotinic Acid and Atorvastatin Calcium Layers for Bilayer Tablets

Ingredients (mg/tablet)	NA1	NA2	NA3	NA4	NA5	NA6	AT
Nicotinic acid layer							
Nicotinic acid	375	375	375	375	375	375	—
Hydroxypropylmethyl cellulose K 100M	30	60	117	105	90	90	—
Microcrystalline cellulose (Avicel PH 112)	75	45	—	—	—	—	—
Starch (Dried)	—	—	—	—	22	22	—
Polyvinylpyrrollidone	15	15	35	35	30	30	—
Talc	3	3	—	—	—	—	—
Magnesium stearate	2	2	—	—	—	—	—
Stearic acid	—	—	5	5	3	3	—
Isopropyl alcohol and methylene chloride	—	—	qs	qs	qs	qs	—
Purified water	qs	qs	—	—	—	—	—
Atorvastatin calcium layer							
Atorvastatin calcium	—	—	—	—	—	—	11.8
Calcium carbonate (light)	—	—	—	—	—	—	45
Lactose	—	—	—	—		—	40.8
Microcrystalline cellulose (Avicel PH 101)	—	—	—	—		—	37.9
Colloidal Silicon Dioxide	—	—	—	—		—	3
Croscarmellose Sodium	—	—	—	—		—	5
Ponceau 4R lake	—	—	—	—		—	0.5
Magnesium stearate	—	—	—	—		—	1.5
Talc	—	—	—	—		—	4.5
Sodium carbonate	—	—	—	—		—	5
Purified water	—	—	—	—		—	qs

Different composition of NA layer (Formulation NA1 to NA6) was tried for optimization of bilayer tablet. qs: quantity sufficient.

ules were passed through #14 sieve. The granules prepared from aqueous granulation were dried at 60 °C for 5 h in a tray drier. The non-aqueous granules were air dried till the loss on drying (LOD) value becomes below 2%. The dried granules were then passed through #20 sieve. To this, the lubricants were added and mixed for 2 min. The tablets of NA1 to NA6 were compressed using 12.7 mm diameter flat circular punch in 16-station compression machine (Cadmach, India).

Preparation of AT Layer The AT, calcium carbonate light, lactose, MCC and croscarmellose sodium (Table 1) passed through #40 sieve and ponceau 4R lake passed through #200 sieve were mixed well in a polybag for 30 min. To this mixture, purified water was added and granulated. The wet granules were passed through #14 sieve and the resultant granules were dried at 60 °C for 5 h in a tray drier. The dried granules were then passed through #20 sieve and to this lubricants, which were previously passed through #40 sieve, were added and mixed well for 2 min.

Bilayer Tablet Compression The tablets of AN1 and AN2 were compressed using 12.7 mm diameter flat circular punch in 27-station bilayer compression machine (Cadmach, India). The lower layer, NA granules were introduced first and a slight pre-compression was made so that the layer was uniformly distributed. After that the second layer AT was added and the final compression was made (Table 2).

***In Vitro* Drug Release Study** The release characteristics of AT was studied using dissolution apparatus USP type II paddle method (TDT-O8L, Electrolab, India) with a stirring speed of 75 rev./min at 37±0.5 °C in 900 ml of phosphate buffer (pH 7.0±0.1) for 45 min. The dissolution samples (10 ml) were collected at an interval of 10, 20, 30 and 45 min with replacement of equal volume of dissolution media and were filtered through a millipore membrane filter. The concentration of AT released at various time intervals were analysed at 248 nm by HPLC.[27] The test was performed in a Luna C18 column using a mobile phase containing acetonitrile : ammonium acetate buffer of pH 4 : tetrahydrofuran at a flow rate of 1.0 ml/min.

The dissolution study of NA was carried out using USP type I (basket) method at a stirring speed of 100 rev./min at 37±0.5 °C in 900 ml of 0.1 N HCl for 2 h followed by study in simulated intestinal fluid (pH 6.8±0.1 phosphate buffer solution) thereafter. The dissolution samples (10 ml) were collected at an interval of 1, 2, 4, 6, 8 and 12 h with replacement of equal volume of dissolution media and were filtered through a membrane filter. The filtrate was collected and the drug release at different time intervals was measured by HPLC.[28] The inertsil ODS column (4.6×150 mm) using a mixture of 0.05 M monobasic sodium phosphate solution (pH 3) and methanol containing 1.5 mM sodium 1-octanesulfonate as the mobile phase at 35 °C were employed and the samples were analyzed at 260 nm. The release studies of both the drugs were conducted in triplicate (6 tablets in each set) and the mean values were plotted *versus* time.

Evaluation of Tablets The tablets were evaluated for hardness, friability, weight variation and thickness and layer separation, if any. The assay and content uniformity were determined by HPLC method. Similarly the NA was assayed by HPLC.

The swelling and erosion studies were performed for optimized formulation AN2 according to the procedure reported in Reynolds, *et al.*[29] Briefly, weighed tablets [H1] were taken on previously weighed watch glass and placed in dissolution vessel, containing 0.1 M hydrochloric acid for first 2 h followed by 6.8 pH phosphate buffer for 4 h using paddle method at stirring speed of 100 rpm. At selected time interval (1 to 6 h) the tablets were withdrawn. The watch glass and tablets were blotted dry to remove water and weighed [H3]. The axial and radial swelling was measured using vernier calipers. The wetted tablets were dried in an oven at 110 °C for 24 h, cooled and dried in a dessicator and finally weighed as dry weight [H2]. The experiment was done in triplicate.

The percent absorption was calculated as

$$A\% = 100[H3 - H2]/H2$$

The percent erosion was calculated as

$$E\% = 100[H1 - H2]/H1$$

Stability Study The tablets of optimized formulation AN2 were Alu-Alu packed and kept for 3 months at 40 °C/75% RH in a stability chamber (Newtronic Walk-in Humidity chamber, India). The tablets were evaluated for physical properties, *in vitro* drug release and assay after 3 months. Content uniformity test was carried out only for AT.

TG/DTA Study The thermogravimetry/differential thermal analysis (TG/DTA) thermogram of pure drug and formulation AN2 were recorded in a TG/DTA analyzer (STA 1500, PL Thermal Sciences, India) at a heating rate of 20 °C/min from 0 to 600 °C in an air atmosphere to characterize drug–excipients interaction.

Results and Discussion

The angle of repose for pure drugs AT and NA were 5.12±0.241 and 3.58±0.156 and hence the poor flow of the pure drugs was exhibited. Also the Carr's index of the pure drugs was found to be high as 26.82±0.523 and 25±0.321 respectively, confirming that both the drugs have poor flow properties and compressibility. Good flow of powders/granules is essential in tableting because the compressibility and flow properties of the drugs are likely to influence the compression process in the preparation of bilayer tablets. In view

of this, the formulations were prepared by wet granulation technique to improve the flow as well as compressibility. The angle of repose was improved to 25.3±0.610 and 29.5± 0.911 and the Carr's index to 11.1±0.310 and 20.83±0.412 respectively for AT and NA.

In the extended release layer of NA to control its release, high viscous polymer HPMC K100M was incorporated in various proportions. The required release profile of NA was fixed to be not more than 50% at the end of 2 h and not less than 90% at the end of 12th hour. In NA1 formulation there was an initial burst release of about 48.9% at 1 h and at 4 h all the drug content was released. This might be due to the depolymerization of HPMC at low pH and/or decreased macromolecular association of the matrix components, thus resulting in decreased consistency of the gel layer formed around the tablet core at the initial hours.[30] Thus, the gel layer on the tablet core with reduced viscosity is more susceptible to erosion and diffusion processes, resulting in rapid drug release in the initial hours. In NA2 formulation also the release at the end of 2 h was found to be more (67.95%). Tablet when comes in contact with the dissolution medium, HPMC absorbs water, swells and become a hydrated gel. At the same time MCC (Avicel PH 101) having disintegration properties, promoted the disintegration of the tablets. The tablets were therefore easy to erode, resulting in a higher release profile.

In NA3, the purified water for preparing coherent mass was replaced with isopropyl alcohol and methylene chloride (1 : 1). The non-aqueous granulation may reduce dissolution and transport of dissolved drug across the diffusion path length. The MCC (Avicel PH 112) was not incorporated and the first 2 h release was brought within the limit (38.62%), but the 12th hour release was only 82.71%. The lubricants magnesium stearate and talc were replaced with stearic acid because it has the low melting point and hence it can avoid the layer separation when compressed as a bilayer tablets. In NA4, HPMC K100M was slightly reduced to increase the 12th hour release. The release became less (79.07%) compared to NA3, but there was no much difference between NA3 and NA4 in the release profile at 12 h. In general, increasing the total polymer content of the tablets decreases the rate of drug release. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug.[31] The quantity of HPMC K100M was further reduced and disintegrant starch was incorporated in NA5. Even then the release at 12 h was found to be less (72.30%). Previous investigations have indicated that changing the compression force had effect on the dissolution rate of drugs from HPMC matrices.[32,33] Hence in NA6 without altering the polymer and its quantity only the compressional force was reduced and thereby hardness got reduced to 6 kg/cm^2 from 9 kg/cm^2. The release at all the hours was found to be satisfactory, that is at 2 h 39.84% and at 12 h 101.73%.

The immediate release layer of AT was prepared as per the composition in Table 1. To maintain the environmental pH, calcium carbonate light was included. The MCC (Avicel PH 101) has the disintegration property when it comes in contact with the dissolution medium and hence it facilitates the tablet to erode. Also the super disintegrant croscarmellose sodium facilitates the same. In the lubricant stage, sodium bicarbonate was added to produce effervescence and thereby enhances the disintegration. After the disintegration of the tablet, lactose present in the granules takes up high amount of water leading to quicker release of drug. The AT layer (Table 1) was compressed as a single layer tablet before compressing as a bilayer and evaluated the release profile. The required 100% release of drug was achieved at 45 min. The same composition was used for bilayer compression and the required release was achieved in one trial that at the end of 45 min 100% of the drug was released (Fig. 2).

Table 2. Composition of Bilayer Tablets

Ingredients (mg/tablet)	NA6+AT=AN1	AN2[a)]
Nicotinic acid layer		
Nicotinic acid	375	375
Hydroxypropylmethyl cellulose K 100M	90	85
Microcrystalline cellulose (Avicel PH 112)	—	—
Starch (dried)	22	22
Polyvinylpyrrolidone	30	25
Talc	—	—
Magnesium stearate	—	—
Stearic acid	3	3
Isopropyl alcohol and methylene chloride	qs	qs
Atorvastatin calcium layer		
Atorvastatin calcium	11.8	11.5
Calcium carbonate (light)	45	45
Lactose	40.8	40.8
Microcrystalline cellulose (Avicel PH 101)	37.9	37.9
Colloidal Silicon Dioxide	3	3
Croscarmellose Sodium	5	5
Ponceau 4R lake	0.5	0.5
Magnesium stearate	1.5	1.5
Talc	4.5	4.5
Sodium carbonate	5	5
Purified water	qs	qs

AN1 and AN2 represents bilayer tablet formulation containing both Nicotinic acid and Atorvastatin calcium layers composition compressed together. *a*) AN2: composition of optimized bilayer tablet subjected for stability study. qs: quantity sufficient.

In AN1, the optimized layer of NA (NA6) and the immediate release layer of AT were compressed together as a bilayer tablet. The 12th hour release of NA became less (81.30%) when compressed as a bilayer tablet. This might be due to the addition of second layer, which would have delayed the interaction of the core with the dissolution medium by reducing the surface available for drug release and by limiting the solvent penetration rate.[34] The polymer and binder quantities were slightly reduced from that of NA6 and compressed along with AT layer to get the formulation AN2 (Table 2). The required release was achieved in AN2. The release kinetics of NA in AN2 was found to be zero order and its regression value was 0.9673±0.02.

The hardness, friability, weight variation, thickness, layer separation, assay and content uniformity were found to be within the limits. In the swelling study the tablets were found swollen and retained their physical integrity till the end. Table 3 shows that there is increase in both percentage water absorbed and percentage erosion of the tablet. But the percentage water absorbed was more dominant than erosion. The release mechanism was more by diffusion than erosion. The fact was further evident from the Higuchi's plot whose regression value was 0.9874±0.11 compared to regression value of Peppa's plot as 0.7544±0.01. In theory, higher the uptake of water by the polymer, more the amount of drug dif-

Table 3. Swelling Behavior of the Optimized Formulations AN2

Time intervals (h)	E%	A%
1	0.1984±0.001	1.5057±0.002
2	0.3917±0.004	1.6981±0.024
3	0.46407±0.004	1.7725±0.005
4	0.64163±0.004	1.9173±0.011
5	0.8673±0.001	2.0954±0.030
6	0.87339±0.002	2.7289±0.348

E%: erosion % of tablet, A%: water absorption % by tablet.

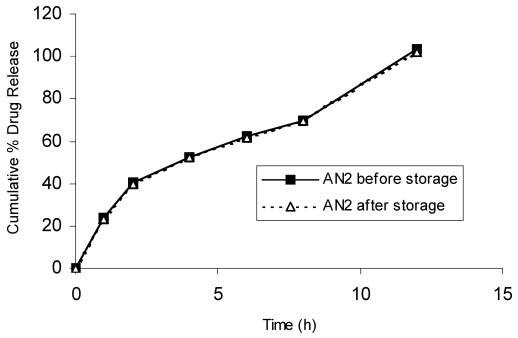

Fig. 1. Comparison of Nicotinic Acid Release Profile from the Optimized Formulation AN2 before and after Storage at 40 °C/75% RH for 3 Months

Each data point represents the average of 6 tablets.

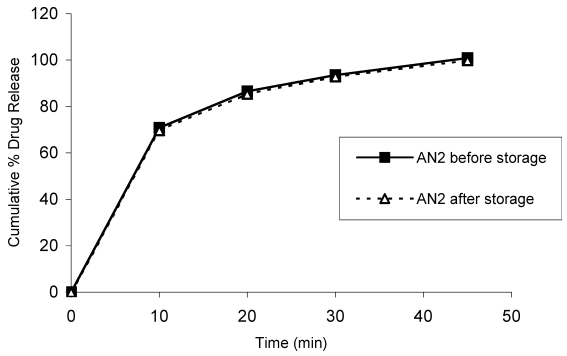

Fig. 2. Comparison of Atorvastatin Calcium Release Profile from the Optimized Formulation AN2 before and after Storage at 40 °C/75% RH for 3 Months

Each data point represents the average of 6 tablets.

fused out from the polymer matrix. Thus the high amount of water uptake by HPMC K100M may lead to considerable swelling of the polymer matrix, allowing drug to diffuse out at a faster rate.[35] For matrix devices, drug is often released by diffusion process such that a receding drug boundary exists within the device.[36] It is also supported by the previous investigation that the slower release rate and greater release duration correlated significantly with greater matrix swelling and negligible erosion.[37]

Based on the results of the *in vitro* drug release studies, the AN2 was considered as the optimized formulation. The formulation showed no change in physical parameters, no degradation peaks in HPLC estimation and drug release pattern was similar after 3 months as before (Figs. 1, 2) subjecting to stability study.

The effect of pharmaceutical excipients on drug release from HPMC based matrix tablets was found to be mainly due to physical interactions between the drug and HPMC.[38] The same is the fact in the present study, which was evident from TG/DTA analysis.

In conclusion the prepared bilayer tablets can be a potential dosage form for delivering AT and NA in an immediate and extended manner.

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