Fabrication and Evaluation of Mini Tablet Filled Capsules for the Prevention of Post Bypass Surgery Heart Stroke

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ABSTRACT

Objective: The work aimed at making mini-tablets filled capsules for the prevention of post bypass surgery heart stroke using Atorvastatin (ATN), and Acetyl Salicylic Acid (ASA).

Methods: The mini-tablets (MTs) of ATN were uncoated, and ASA was enteric-coated. A novel approach was adopted in tackling gastric irritation of ASA, by using Plantago ovata seed mucilage as a binder in making the MTs. MTs of ATN and ASA were placed in capsules. ATN and ASA compatibility with excipients used were checked by DSC and FTIR studies. All prepared MTs were prosecuted for post-compression constraints.

Results: The prepared MTs confirmed no interaction by FTIR and DSC studies. All the MTs passed the physicochemical constraints. ATN was released within 60 min, whereas enteric-coated ASA, showed its resistance to release in an acidic environment (2h) and favour in an alkaline buffer (within 45 min).

Conclusion: The study concludes that by using P. ovata as a binder in making tablets will resolve the issues related to gastric irritation.

Key Words: Mini-tablets, Atorvastatin, Plantago ovata, Gastric irritation

INTRODUCTION

Many fixed-dose combination therapies prescribed to tackle heart stroke after bypass surgery, among them Atorvastatin (ATN) and Acetyl Salicylic Acid (ASA) combination is a popular choice.1 ATN is an HMG-CoA reductase inhibitor that slows down cholesterol manufacture in the body, and in term prevents its accumulation in blood capillaries, majorly the vital organs like the heart and the brain.2 Additionally, ATN reduces low-density lipoproteins and Cholesterol and in term increases high-density lipoproteins.3 ASA has anti-platelet action at a lower dose and popularly prescribed for preventing recurrent development of blood clots.4

Longterm therapy of ASA, causes stomach ulcers5 that can be prevented by co-administration of proton pump inhibitors (PPIs). But many clinical studies revealed that ATN and ASA interact with PPIs.6,7 Mini-tablets (MTs) are tiny tablets which are uniform in shapes, sizes, and weights. Wide varieties of MTs can be easily filled in capsules for attaining the anticipated effects.8 They are desired to owe their uniformity in drug, sizes, ease of preparation, and low cost equated to pellets and granules.9 A few attempts were made by giving PPTs for patients with ATN and ASA therapy but raised the issues related to drug compatibilities.10,11 So, a need came to resolve such issues, the authors made an innovative effort to add some gastroprotective excipients during formulation. By doing an extensive literature survey the authors found P. ovata mucilage has gastric protective activity12, 13 and tablet binder properties.14, 15

In this investigation, the authors used P. ovata seed mucilage as a binder during tablet granulation, and compressed them into MTs (uncoated ATN and enteric-coated ASA), and filled into capsules.

MATERIALS AND METHODS

Materials
Atorvastatin was gifted from USV Pvt. Ltd, Mumbai, Acetyl-salicylic acid from Waksman Selman pharmaceutical Pvt Ltd

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Anantapur, AP, India. Lactose, MCC, Magnesium stearate, Talc, Ethylcellulose, and HPMC Phthalate were purchased from Qualigens, Fine chemicals, Mumbai. Empty hard gelatin capsules (size ‘1’) were gifted from Hetero drugs, Hyderabad, Telangana. The remaining ingredients used were of AR grade.

Preformulations Investigations

**Fourier Transform Infrared (FTIR) spectral analysis**
The matching of ATN and ASA with excipients used in this study was done with a sample (2 mg) mixed with 200 mg of KBr, compressed to pellet, and scanned (400-4000 cm⁻¹) with a resolution of 1 cm⁻¹ (Perkin Elmer, Spectrum-100, Japan).

**DSC studies**
DSC thermograms of ATN, and ASA; and their mixture with excipients were documented using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan), by heating (30-350°C) with 10°C/min rate.

### Table 1: Composition of various ATN mini-tablets

| Ingredient                  | ATM-1 | ATM-2 | ATM-3 | ATM-4 | ATM-5 | ATM-6 | ATM-7 | ATM-8 | ATM-9 |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Atorvastatin                | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    |
| MCC                         | 52    | 47    | 42    | 37    | 32    | 27    | 22    | 17    | 12    |
| Lactose                     | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    |
| P. ovata seed mucilage      | 5     | 10    | 15    | 20    | 25    | 30    | 35    | 40    | 45    |
| Magnesium stearate          | 2     | 2     | 2     | 2     | 2     | 2     | 2     | 2     | 2     |
| Talc                        | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     |
| Weight of the tablet        | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |

### Preparation of ASA enteric-coated MTs
The enteric-coated tablets for delayed-release have these steps.\(^{19,20}\)

### Table 2: Composition of various ASA mini-tablets

| Ingredient                  | ASM-1 | ASM-2 | ASM-3 | ASM-4 | ASM-5 | ASM-6 | ASM-7 | ASM-8 | ASM-9 |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Aspirin                     | 75    | 75    | 75    | 75    | 75    | 75    | 75    | 75    | 75    |
| MCC                         | 107   | 102   | 97    | 92    | 87    | 82    | 77    | 72    | 67    |
| Lactose                     | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    |
| P. ovata mucilage           | 5     | 10    | 15    | 20    | 25    | 30    | 35    | 40    | 45    |
| Magnesium stearate          | 2     | 2     | 2     | 2     | 2     | 2     | 2     | 2     | 2     |
| Talc                        | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     |
| Weight of the tablet        | 200   | 200   | 200   | 200   | 200   | 200   | 200   | 200   | 200   |

**Experimental Methods**

**Isolation of P. Ovata seeds mucilage**
The P. Ovata seeds were drenched in distilled water (~20 times) for 48 h, boiled for 10 min (for the discharge of mucilage). Later passed through a muslin cloth (mucile removed) and the filtrate was collected. Acetone was added in equal proportion (mucilage precipitates). Then the mucilage was detached and dried in an oven (<60°C), crushed, sieved (# 80 mesh), weighed, and stored in a desiccator.\(^{16,17}\)

**Preparation of mini-tablets**

**Preparation of Atorvastatin MTs**
The ingredients (Table 1) screened (#40 mesh), and mix for 3 min. To this blend magnesium stearate and talc (screened #60) were added and mixed in the polybag for 3 min. The blend was compressed to get MTs.\(^{18}\)

**Preparation of core tablet**
The ingredients (Table 2) screened (#40 mesh), and adopted the same method of how ATN MTs were prepared.
Sub coating of ASA
The core tablets so formed were made water-proof by sub coating (Table 3).

Table 3: Sub Coating for ASA Tablets

| Ingredient/tablet     | Quantity |
|-----------------------|----------|
| Ethylcellulose        | 2.0      |
| Isopropyl alcohol     | q.s      |
| Dichloromethane       | q.s      |

Enteric coat composition
The waterproofed subcoated tablets were subjected to gastric resistant enteric coating (Table 4).

Table 4: Enteric Coating for Aspirin DR Tablets

| Ingredient/tablet      | Quantity |
|-----------------------|----------|
| HPMC phthalate-55     | 1.422    |
| Triethyl citrate      | 0.142    |
| Talc                  | 0.355    |
| Dichloromethane       | q.s      |
| Methanol              | q.s      |

Filling of mini-tablets in capsule
Three MTs each of ATN, and ASA were filled manually into capsule bodies and closed with a cap, and coded (Table 5). The junction between the capsule body and cap was sealed by applying water with a micro brush.

Table 5: Capsule formulations

| Formulation | MTFC-1 | MTFC -2 | MTFC -3 | MTFC -4 | MTFC -5 | MTFC -6 | MTFC -7 | MTFC -8 | MTFC -9 |
|-------------|--------|---------|---------|---------|---------|---------|---------|---------|---------|
| ATM-1       | ATM-2  | ATM-3   | ATM-4   | ATM-5   | ATM-6   | ATM-7   | ATM-8   | ATM-9   |
| ASM-1       | ASM-2  | ASM-3   | ASM-4   | ASM-5   | ASM-6   | ASM-7   | ASM-8   | ASM-9   |

MFTC-Mini-tablet filled capsule; ATM- Atorvastatin mini-tablets; ASM- Acetylsalicylic Acid mini-tablets

Evaluation of Mini-Tablets

Pre-compression parameters
Bulk and tapped densities, Carr’s index, Hausner’s ratio, and angle of repose were appraised for the blend of MTs.

Post-compression parameters
Parameters like thickness, hardness, weight variation, friability, etc. were appraised for the prepared MTs.

Weight variation of mini-tablets
The weight of 20 MTs was individually weighed (MODELS, CAS-54), and the mean was calculated and the deviation was calculated.

Diameter and thickness for mini-tablets
10 randomly selected MTs from each batch were logged with a Vernier calliper, and mean was documented.

Mini-tablet crushing strength/ hardness test
Crushing strength of the 6 MTs individually measured using the Pfizer tablet hardness tester (mLabs-SE-276(B). Each MT is individually placed between the jaws and pressed till it crushes, and the mean was recorded.

Friability test for mini-tablets
Ten MTs of ATN were placed in a Friability tester (Veego, VFT-2D) and rotated at 25 rpm for a total of 100 rotations.

The loss on friability can be obtained from the initial and final weights of MTs. On the other hand, this test is not required for MTs of ASA (as they are enteric-coated).

Disintegration test
The uncoated 6 MTs of ATN were kept in disintegration apparatus (0.1M HCl) at 37±2.0°C and the time for the breakdown was noted down. Moreover, the enteric-coated MTs of ASA the same procedure was followed, after 2h, the medium was replaced by 6.8 pH, PBS for 30 min.

Uniformity of drug content
10 MTs of ATN were weighed and powdered. A quantity of 75 mg of ATN was dissolved in 0.1 N HCl (100 ml). Then the solution was filtered, diluted suitably and analyzed using UV/visible spectrophotometer at 230 nm. For ASA, 10 MTs of ASA were weighed, triturated in a mortar. A 100 mg of ASA was transferred to a 50 ml volumetric flask, diluted by 20 ml of diluting solution (acetonitrile and formic acid 99:1). The volumetric flask was shaken manually, centrifuged at 3000 rpm for 5 min and then the stock prepared was diluted. An aliquot of the diluted solution was inserted into a liquid chromatograph with a detector set at 230 nm. The responses were compared with the standard to find the quantity in mg of ASA present in the sample. Table 6 shows the chromatographic settings for ATN and ASA estimation.
Table 6: The chromatographic conditions for the assessing ATN and ASA

| Chromatographic Conditions | Specification |
|---------------------------|---------------|
| Apparatus                | HPLC          |
| Column                   | C18, 250 x 4.6, 5µ (Inertsil) |
| Wavelength (nm)          | 230 (isobestic) |
| Detector                 | UV/PDA        |
| Injection volume         | 20µl          |
| Flow rate                | 1.5ml/min     |
| Sample cooler temp       | Ambient(25°C) |
| Run Time                 | 10 min        |
| Elution                  | Isocratic     |

In-vitro Dissolution Studies

The dissolution conditions for ATN as explained (Table 7).

Table 7: Dissolution conditions fused in the study

| Description | ATN | ASA |
|-------------|-----|-----|
| Apparatus   | Dissolution Apparatus USP Type II (Paddle) | 0.1N HCl for 2h, and then Phosphate buffer (pH 6.8) for next 45 min |
| Medium      | 0.1 M HCl | 0.1N HCl |
| Medium Volume | 900 ml | 900 ml |
| Speed       | 50 RPM | 100 |
| Sampling intervals | 5, 10, 20, 30, 45, and 60 min | 30 min, 1 and 2h (in 0.1m HCl); 5, 10, 20, 30, 45, and 60 min (6.8 buffer) |
| Temperature | 37 ± 0.5°C | 37 ± 0.5°C |

Kinetic treatment of the dissolution data

The dissolution data were further treated to find the best fit kinetic model and to know the possible release pattern.

RESULTS AND DISCUSSION

The thermogram of ATN showed an endothermic peak at 160.02°C, and it combined with excipient showed a shift in thermogram was observed with a peak of 156.41°C (Figure 1). Whereas the thermogram of ASA showed an endothermic peak at 134.18°C, and it combined with excipient showed a shift in thermogram was observed with a peak of 123.88°C (Figure 2). This data confirms the impregnation of drugs with excipients used.

The FTIR spectra revealed that the characteristic peaks and stretches of ATN were found even in the blend, indicates compatibility confirmations of ATN with excipients (Figure 3). Similarly, the peaks and stretches of the ASA spectrum were found even in the blend (Figure 4), indicates compatibility confirmations of ASA with excipients.
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The ATN blend showed an angle of repose, Carr’s compressibility index, and Hausner ratio values less than 30°, 10%, and 1.25 respectively, which indicates the good flow properties (Table 8), similarly, ASA blend was also proved its good flow properties (Table 9).

The MTs were subjected to various parameter assessments viz., Uniformity of weight, hardness, thickness, friability, and assay. The outcomes of these strictures exhibited nearly uniform thickness in all the formulations. The weights of all MTs within the ±7.5% (standard value for tablets weight ranged 80-250mg) and passed the uniformity of weight as per official requests. All the tablets showed sufficient strength or hardness (>4Kg/cm²), representing physical strength for which required during handling & transport. The hardness is not an absolute gauge of strength, so friability was also performed and the loss on friability was <1% for all MTs (acceptable limit). The conventional uncoated MTs of ATN were disintegrated within 15 min (900 sec), whereas the enteric-coated MTs of ASA did not show any sign of disintegration in 0.1 M HCl for 2h, and disintegrated within 45 min (2700 sec) in pH 6.8 buffer, which proves the enteric coating efficiency of ASA enteric-coated MTs.

An appreciable uniformity in ATN and ASA content were observed among different batches of MTs and the % of drug content was more than 95% (Table 10 and 11).

Table 8: Flow character specifications of ATN blend

| Formulation | Angle of repose (°) | LBD  | TBD  | CI   | HR   |
|-------------|---------------------|------|------|------|------|
| ATM-1       | 27.84±0.04          | 0.786±0.06 | 0.799±0.02 | 1.630±0.02 | 1.017±0.03 |
| ATM-2       | 29.25±0.02          | 0.453±0.04 | 0.469±0.06 | 3.419±0.03 | 1.036±0.02 |
| ATM-3       | 29.68±0.02          | 0.326±0.07 | 0.333±0.02 | 2.109±0.04 | 1.022±0.02 |
| ATM-4       | 30.02±0.02          | 0.366±0.02 | 0.389±0.04 | 5.928±0.09 | 1.064±0.02 |
| ATM-5       | 29.12±0.06          | 0.453±0.03 | 0.470±0.02 | 3.625±0.02 | 1.038±0.02 |
| ATM-6       | 28.25±0.04          | 0.527±0.02 | 0.567±0.06 | 6.714±0.06 | 1.072±0.01 |
| ATM-7       | 28.69±0.02          | 0.370±0.02 | 0.404±0.02 | 8.437±0.05 | 1.093±0.02 |
| ATM-8       | 28.27±0.05          | 0.583±0.05 | 0.613±0.06 | 4.902±0.03 | 1.052±0.02 |
| ATM-9       | 28.91±0.02          | 0.699±0.02 | 0.704±0.05 | 0.712±0.02 | 1.008±0.05 |

Values in mean ±SD; trials (n=3)

Table 9: Flow character specifications of ASA blend

| Formulation | Angle of repose (°) | LBD  | TBD  | CI   | HR   |
|-------------|---------------------|------|------|------|------|
| ASM-1       | 29.98±0.05          | 0.259±0.02 | 0.269±0.03 | 3.732±0.04 | 1.039±0.01 |
| ASM-2       | 29.05±0.04          | 0.529±0.04 | 0.537±0.02 | 1.493±0.02 | 1.016±0.02 |
| ASM-3       | 28.41±0.02          | 0.569±0.05 | 0.579±0.06 | 1.731±0.02 | 1.018±0.01 |
| ASM-4       | 28.19±0.01          | 0.525±0.02 | 0.546±0.04 | 3.854±0.02 | 1.041±0.02 |
| ASM-5       | 29.36±0.02          | 0.452±0.02 | 0.459±0.01 | 1.525±0.04 | 1.015±0.03 |
| ASM-6       | 28.52±0.03          | 0.548±0.02 | 0.556±0.04 | 1.622±0.05 | 1.017±0.05 |
| ASM-7       | 26.39±0.02          | 0.256±0.05 | 0.260±0.02 | 1.931±0.02 | 1.020±0.02 |
| ASM-8       | 28.25±0.01          | 0.526±0.01 | 0.542±0.02 | 3.143±0.03 | 1.033±0.01 |
| ASM-9       | 27.15±0.02          | 0.660±0.01 | 0.667±0.02 | 1.202±0.02 | 1.013±0.02 |

Values in mean ±SD; trials (n=3)
Table 10: Physical Characteristics of ATN MTs

| Formulation | Uniformity of weight (mg) | Hardness (cm²) | Thickness (mm) | Friability (%) | Disintegration (sec) | Assay (%) |
|-------------|---------------------------|----------------|----------------|----------------|---------------------|-----------|
| ATM-1       | 100.1±1.82                | 6.3±0.07       | 3.02±0.02      | 0.11±0.01      | 248±4              | 99.01±2.65 |
| ATM-2       | 100.2±1.65                | 5.9±0.03       | 3.00±0.02      | 0.24±0.02      | 266±5              | 96.12±2.09 |
| ATM-3       | 99.9±2.30                 | 6.8±0.02       | 3.01±0.02      | 0.55±0.03      | 270±6              | 97.38±1.28 |
| ATM-4       | 99.8±1.54                 | 7.4±0.01       | 3.00±0.01      | 0.18±0.01      | 209±2              | 95.38±0.19 |
| ATM-5       | 100.1±2.49                | 9.5±0.02       | 3.00±0.02      | 0.16±0.01      | 308±4              | 97.46±3.16 |
| ATM-6       | 100.2±2.46                | 6.0±0.06       | 2.98±0.01      | 0.17±0.01      | 219±5              | 98.69±3.26 |
| ATM-7       | 100.1±1.65                | 8.2±0.07       | 2.99±0.01      | 0.19±0.01      | 260±4              | 98.15±1.25 |
| ATM-8       | 100.2±1.25                | 6.1±0.03       | 3.01±0.01      | 0.22±0.02      | 284±3              | 96.07±3.25 |
| ATM-9       | 100.1±1.24                | 8.6±0.02       | 3.00±0.02      | 0.10±0.01      | 279±3              | 97.15±1.24 |

Values in mean ±SD; trials made (n=3)

Table 11: Physical Characteristics ASA MTs

| Formulation | Uniformity of weight (mg) | Hardness (cm²) | Thickness (mm) | Disintegration (sec) of 0.1M HCl (2h) | pH 6.8 | Assay (%) |
|-------------|---------------------------|----------------|----------------|--------------------------------------|--------|-----------|
| ASM-1       | 200.34±1.09               | 5.7±0.04       | 3.00±0.02      | 0.00                                 | 356±6  | 98.54±1.65 |
| ASM-2       | 201.20±1.65               | 6.5±0.02       | 3.01±0.01      | 0.00                                 | 312±8  | 98.02±1.95 |
| ASM-3       | 200.25±1.73               | 7.1±0.06       | 2.99±0.02      | 0.00                                 | 369±7  | 96.36±2.48 |
| ASM-4       | 201.98±2.15               | 5.6±0.05       | 3.01±0.01      | 0.00                                 | 377±5  | 99.25±1.65 |
| ASM-5       | 200.87±1.46               | 8.2±0.01       | 3.01±0.02      | 0.00                                 | 333±9  | 98.26±1.66 |
| ASM-6       | 200.58±1.68               | 7.2±0.02       | 3.00±0.01      | 0.00                                 | 355±8  | 98.85±1.26 |
| ASM-7       | 200.39±1.84               | 6.9±0.06       | 3.01±0.02      | 0.00                                 | 381±5  | 99.64±2.22 |
| ASM-8       | 199.32±2.15               | 7.5±0.07       | 3.00±0.01      | 0.00                                 | 394±6  | 98.16±2.34 |
| ASM-9       | 199.28±2.12               | 6.8±0.03       | 3.01±0.01      | 0.00                                 | 365±3  | 98.29±2.36 |

Values in mean ±SD; trials made (n=3)

More than 75% of ATN was released within 60 min (uncoated) (Figure 5). On the other hand, the enteric-coated MTs of ASA were not shown any sign of dissolution in 0.1 M HCl for 2h and >75% dissolved within 45 min in pH 6.8 buffer (Figure 6), which reveals the firmness of the enteric coat on MTs of ASA.

Figure 5: Zero-order release plots for ATN mini-tablets.

Figure 6: Zero-order release plots for ASA mini-tablets.

The mechanism of drug release from the formulations when tried to fit Zero order, First order, Higuchi, Korsmeyer Pep-pa’s, and Hixon Crowell’s plots. The regression and interpretation of release exponent value (n) were assessed and graphically represented in Figures 7 (A, B, C, and D) and 8 (A, B, C, and D). Based on these dates, it was confirmed Higuchi’s model is best fit and the release was non-fiction for all ATN MTs, whereas for ASA formulations i.e., ASM-4,
ASM-5, ASM-6, and ASM-7 followed fiction and remaining ASA formulations followed non-fiction release.

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CONCLUSION

The distinct mini-tablets of uncoated Atorvastatin and enteric-coated Acetyl Salicylic Acid were effectively made, filled in capsules, and recapped. The gastric irritation caused by Acetylsalicylic acid is encountered with the addition of Plantago ovata seed mucilage as a tablet binder (as it already proved for its gastric protective actions). Thus, mini-tablets filled capsules of Atorvastatin and Acetyl Salicylic Acid for treating post bypass surgery heart stroke, without any gastric irritation.

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