Investigation of Drug-Excipient Compatibility Studies Using Validated RP-HPLC Method for Azelnidipine and Telmisartan Tablets

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ABSTRACT

Aims: The Drug-Excipient compatibility testing was conducted at an early product development stage to determine that Excipients were compatible with drugs used in formulation and to distinguish as many degradation products as possible using validated gradient RP-HPLC method.

Study Design: Drug-Excipient Compatibility study was conducted in glass vials at different stability conditions namely, at 30°C ± 2°C/75% ± 5% RH, 40°C ± 2°C/ 70% ± 5% RH for 04 weeks and another set of closed vials were stored in stability chamber at temperature 60°C ± 2°C for 02 weeks.

Methodology: Samples were analyzed by validated RP-HPLC method using Inertsil C-18 Column 150 x 4.6 mm ×5 µm, column oven temperature 40°C, flow rate 1.5 mL/min, Injection volume 10 µL with run time 12.0 minutes at 254 nm using Acetonitrile and buffer as mobile phase in gradient mode.

Results: The developed method meets all system suitability parameters and found specific to determine the drug in the presence of Excipient as no interference was observed at the Retention time (Rt) of analyte.

Conclusion: There was no physical and chemical incompatibility observed with Drug-Excipient and did not observe significant increase in the related substances.
1. INTRODUCTION

Drug-Excipient compatibility method was developed by which possible stability problems occur due to interaction of drug substances with excipients in finished formulation can be forecast [1]. Drug-excipient compatibility study is an essential in the preformulation phase of the progress of all dosage forms.[2] The probable physical and chemical interactions of drugs and excipients can change the physical, chemical, therapeutic property and constancy of the dosage form. Drug-excipient compatibility study provides the details of drug degradation, mechanism of drug-excipient interaction like physical, chemical and biopharmaceutical.[3] Various thermal and non-thermal method of analysis, are used to detect incompatibility between drug and excipient.[4] When the nature of interaction is determined further steps can be taken to improve the stability of drug and its dosage form. From these studies, we can conclude that consequential use of thermal and non-thermal method provides data for drug-excipient interaction which help in assortment of excipient for the improvement of stable dosage form. In addition to examine the interactions between the API and the excipients, the effect of factors such as humidity and temperature is explored in these studies. Such factors are known to speed up the degree of drug-excipient interactions by changing the physico-chemical properties or rate of degradation of the drugs and excipients.[5-6] During these studies bulk drug and excipients comes into contact with each other as physical admixtures in a fixed ratio, or as a preliminary dosage form; subject to several stress conditions. The physico-chemical and performance attributes of the bulk drug and excipients are then estimated using one or more analytical techniques [7-11].

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Azelnidipine (potency 99.58%), and Telmisartan (potency 99.66%) working standards were received as gift samples from M/s. Synokem Pharmaceuticals Limited, Haridwar, Uttarakhand. Microcrystalline cellulose (diluent), Meglumine (solubilizer), Lactose (diluent), Cross-providone (disintegrant), sodium lauryl sulfate (surfactant) and magnesium stearate (lubricant) were used as excipients in formulation of Azelnidipine 8 mg and Telmisartan 40 mg tablets. Acetonitrile, Methanol were of HPLC grade and reagents like Ammonium dihydrogen orthophosphate, Orthophosphoric acid, Sodium Hydroxide, were Analytical grade and Milli-Q water for buffer preparation was obtained from M/s. Kimia Biosciences Limited, Gurugram, Haryana.

2.2 HPLC Method Development

2.2.1 Chromatographic conditions and instrument

HPLC instrument (Agilent make, model-LC-1210 with empower software) equipped with Photodiode-Array Detection (PDA) detector was used with Inertsil C-18 column 150×4.6 mm, 5 µm particle size at temperature 40°C. The flow rate of mobile phase was at 1.5 mL/min in gradient mode, λ max 254 nm, injection volume 10 µL and run time of analytical method was 12 mins.

Table 1. Gradient program

| Time  | Pump A % (Acetonitrile) | Pump B % (Buffer) |
|-------|------------------------|-------------------|
| 0.01  | 45                     | 55                |
| 3.00  | 45                     | 55                |
| 5.00  | 30                     | 70                |
| 7.00  | 30                     | 70                |
| 8.00  | 45                     | 55                |
| 12.00 | 45                     | 55                |

2.2.2 Preparation of Buffer solution

Accurately weighed and transferred the 4.0 gm of Ammonium dihydrogen orthophosphate in to 2000 mL of HPLC grade water, mixed well and sonicated till dissolved. Adjusted the pH of buffer to 3.0 ± 0.05 with dilute Ortho-phosphoric acid and filtered through 0.45 pm PVDF membrane filter and degassed.

2.2.3 Preparation of Diluent/ Blank solution

The buffer and Acetonitrile (25:75 % v/v) was mixed and sonicated, and same used as blank solution.

2.2.4 Preparation of stock and standard solutions

The stock solution of Azelnidipine and Telmisartan was prepared by transferring the pre-weighed quantities 40.25 mg of Azelnidipine and 200.30 mg of Telmisartan in to 100 mL volumetric flask. About 60 mL diluent (Buffer: Acetonitrile 25:75 % v/v) was added to the flask and sonicated, and final volume was adjusted to

Keywords: Azelnidipine; Telmisartan; RP-HPLC; drug-excipient compatibility study; method validation.
100 mL. From this stock solution, 10 mL of solution was transferred into 100 mL volumetric flask and the final volume was made up with diluent to get final concentration 40.08 µg/mL of Azelnidipine and 199.62 µg/mL of Telmisartan. The final standard solution was obtained after filtering through 0.45 µm PVDF membrane filter.

2.2.5 Storage and Analysis of samples

Prepare Drug: Excipient compatibility samples and charging for stability at different stability conditions 30°C ± 2°C/75% ± 5% RH, 40°C ± 2°C/75% ± 5% RH for 04 weeks and 60 ± 2°C for 02 weeks and then analyzed for physical (appearance, color etc.) and chemical stability. Accurate amount of drug and excipient were mixed and placed in glass vials. Each vial was labeled with the amount of drug and excipient. The total weight of drug excipient blend in a vial was usually kept at about 2 gm & 3 gm (Drug: Excipient in 1:1 ratio & 1:1:1 ratio.) The above samples of Drug-Excipient mixtures were analyzed at the end of above mentioned time interval by using validated RP-HPLC method.

3. RESULT AND DISCUSSION

3.1 System Suitability

System suitability parameters were performed by injecting blank in single and six replicate injections of standard solution (Fig. 1, 2). The % RSD for area and Rt of Azelnidipine and Telmisartan peak obtained from six replicate standard injections should be not more than (NMT) 2.0, Tailing Factor NMT 2.0, Theoretical Plates NLT 2000 and Resolution factor not less than (NLT) 2.0., obtained results were presented in Table 2.

3.2 Specificity

Specificity of the developed method was measured to analyze response in presence of any interfering factors (like excipients, related substances etc.). There was no any interference from blank, placebo and excipients at the retention time of Azelnidipine and Telmisartan peak. Retention time of main peak from sample preparation should be similar to that of standard preparation.

3.3 Analysis of Drug-Excipient Samples

Drug-Excipient mixtures were analyzed by using validated RP-HPLC method (Fig. 3-8). After performing System Suitability and Specificity, samples were analyzed with freshly prepared standard solution.
| Injection | AREA (A) | RT (A) | USP Tailing Factor (A) | USP Theoretical Plates (A) | USP Resolution (A) | AREA (B) | RT (B) | USP Tailing Factor (B) | USP Theoretical Plates (B) | USP Resolution (B) |
|-----------|---------|--------|------------------------|---------------------------|---------------------|---------|--------|------------------------|---------------------------|---------------------|
| 1         | 483521  | 97685  | 2.273                  | 4.722                     | 1.06                | 1.01    | 5396               | 9939                     | -                    | 15.40               |
| 2         | 485633  | 98511  | 2.274                  | 4.720                     |                     |         |                    |                          |                      |                     |
| 3         | 484627  | 99002  | 2.274                  | 4.723                     |                     |         |                    |                          |                      |                     |
| 4         | 485223  | 98046  | 2.275                  | 4.725                     |                     |         |                    |                          |                      |                     |
| 5         | 484564  | 98569  | 2.274                  | 4.723                     |                     |         |                    |                          |                      |                     |
| 6         | 484120  | 98119  | 2.276                  | 4.727                     |                     |         |                    |                          |                      |                     |
| Average   | 484614.67 | 98322 | 2.27                    | 4.72                      |                     |         |                    |                          |                      |                     |
| Standard deviation | 755.06 | 465.25 | 0.00                    | 0.00                     |                     |         |                    |                          |                      |                     |
| % RSD     | 0.16    | 0.47   | 0.05                    | 0.05                      |                     |         |                    |                          |                      |                     |
| % RSD Limit | NMT 2.0 % |        |                        |                          |                     |         |                    |                          |                      |                     |

Table 2. Results of system suitability parameters

| Sr. No. | Drug: Excipient | Physical Observations |
|---------|-----------------|-----------------------|
|         | Initial | 30°C ± 2°C & RH 75% ± 5% (4 Weeks) | 40°C ± 2°C & RH 75% ± 5% (4 Weeks) | 60°C ± 2°C (2 Weeks) |
| 1       | Azelnidipine   | Complies              | Complies                  |                     |
| 2       | Telmisartan    | Complies              | Complies                  |                     |
| 3       | Azelnidipine + Telmisartan | Complies | Complies                  |                     |
| 4       | Azelnidipine + Microcrystalline cellulose (MCC) | Complies | Complies                  |                     |
| 5       | Azelnidipine + Lactose (L) | Complies | Complies                  |                     |
| 6       | Azelnidipine + Crospovidone (CP) | Complies | Complies                  |                     |
| 7       | Azelnidipine + Magnesium Stearate (MS) | Complies | Complies                  |                     |
| 8       | Telmisartan+ Microcrystalline cellulose (MCC) | Complies | Complies                  |                     |
| 9       | Telmisartan + Lactose (L) | Complies | Complies                  |                     |
| 10      | Telmisartan + Crospovidone (CP) | Complies | Complies                  |                     |
| 11      | Telmisartan + Magnesium Stearate (MS) | Complies | Complies                  |                     |
| 12      | Azelnidipine + (MCC) + (L) + (CP) + (MS) | Complies | Complies                  |                     |
| 13      | Telmisartan + (MCC) + (L) + (CP) + (MS) | Complies | Complies                  |                     |
| 14      | Azelnidipine + Telmisartan + (MCC) + (L)+(CP) + (MS) | Complies | Complies                  |                     |

Table 3. Physical observations of drug-excipient compatibility (Pack Size 5.0 mL Glass Vial)

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Table 4. Chemical observations of drug-excipient compatibility at pack size 5.0 ml glass vial at long term stability (temperature 30°C + 2°C & RH 75% + 5%)

| Sr. No. | Drug: Excipient | Chemical Observations | Initial | 30°C + 2°C & RH 75% + 5% (4 Weeks) |
|---------|-----------------|-----------------------|---------|------------------------------------|
|         |                 |                       | Any Individual Impurity | Total Impurities | Any Individual Impurity | Total Impurities |
| Impurities Limits | NMT 1.0% | NMT 2.0% | NMT 1.0% | NMT 2.0% |
| 1.       | Azelnidipine    | 0.055                 | 0.108    | 0.059                             | 0.112               |
| 2.       | Telmisartan     | 0.021                 | 0.052    | 0.024                             | 0.056               |
| 3.       | Azelnidipine+ Telmisartan | 0.057         | 0.109    | 0.063                             | 0.113               |
| 4.       | Azelnidipine + Microcrystalline cellulose (MCC) | 0.056 | 0.108 | 0.059 | 0.112 |
| 5.       | Azelnidipine+ Lactose (L) | 0.055 | 0.109 | 0.059 | 0.111 |
| 6.       | Azelnidipine+ Crospovidone (CP) | 0.056 | 0.109 | 0.058 | 0.112 |
| 7.       | Azelnidipine + Magnesium Stearate (MS) | 0.057 | 0.110 | 0.059 | 0.113 |
| 8.       | Telmisartan+ Microcrystalline cellulose (MCC) | 0.057 | 0.108 | 0.061 | 0.112 |
| 9.       | Telmisartan + Lactose (L) | 0.021 | 0.052 | 0.025 | 0.056 |
| 10.      | Telmisartan + Crospovidone (CP) | 0.022 | 0.052 | 0.026 | 0.059 |
| 11.      | Telmisartan + Magnesium Stearate (MS) | 0.024 | 0.049 | 0.024 | 0.058 |
| 12.      | Azelnidipine + (MCC) + (L) + (CP) + (MS) | 0.020 | 0.053 | 0.026 | 0.060 |
| 13.      | Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.021 | 0.054 | 0.028 | 0.058 |
| 14.      | Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.022 | 0.053 | 0.027 | 0.058 |

Table 5. At Accelerated Stability (Temperature 40°C ± 2°C & RH 75% ± 5%)

| Sr. No. | Drug: Excipient | Chemical Observations | Initial | 40°C ± 2°C & RH 75% ± 5% (4 Weeks) |
|---------|-----------------|-----------------------|---------|------------------------------------|
|         |                 |                       | Any Individual Impurity | Total Impurities | Any Individual Impurity | Total Impurities |
| Impurities Limits | NMT 1.0% | NMT 2.0% | NMT 1.0% | NMT 2.0% |
| 1.       | Azelnidipine    | 0.055                 | 0.108    | 0.062                             | 0.115               |
| 2.       | Telmisartan     | 0.021                 | 0.052    | 0.032                             | 0.065               |
| 3.       | Azelnidipine+ Telmisartan | 0.057         | 0.109    | 0.060                             | 0.116               |
| 4.       | Azelnidipine + Microcrystalline cellulose (MCC) | 0.056 | 0.108 | 0.062 | 0.116 |
| 5.       | Azelnidipine+ Lactose (L) | 0.055 | 0.109 | 0.063 | 0.117 |
| 6.       | Azelnidipine+ Crospovidone (CP) | 0.056 | 0.109 | 0.060 | 0.116 |
| 7.       | Azelnidipine + Magnesium Stearate (MS) | 0.057 | 0.110 | 0.064 | 0.116 |
| 8.       | Telmisartan+ Microcrystalline cellulose (MCC) | 0.057 | 0.108 | 0.064 | 0.115 |
| 9.       | Telmisartan + Lactose (L) | 0.021 | 0.052 | 0.064 | 0.117 |
| 10.      | Telmisartan + Crospovidone (CP) | 0.022 | 0.052 | 0.065 | 0.116 |
| 11.      | Telmisartan + Magnesium Stearate (MS) | 0.024 | 0.049 | 0.064 | 0.114 |
| 12.      | Azelnidipine + (MCC) + (L) + (CP) + (MS) | 0.020 | 0.053 | 0.065 | 0.116 |
| 13.      | Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.021 | 0.054 | 0.066 | 0.117 |
| 14.      | Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.022 | 0.053 | 0.066 | 0.116 |
Table 6. At temperature 60°C± 2°C (2 Weeks)

| Sr. No. | Drug: Excipient | Initial | At Temperature 60°C± 2°C (2 Weeks) |
|---------|----------------|---------|-----------------------------------|
|         |                | Initial | At Temperature 60°C± 2°C (2 Weeks) |
|         |                | Impurities Limits | NMT 1.0% | NMT 2.0% | NMT 1.0% | NMT 2.0% |
| 1.      | Azelnidipine   | 0.055   | 0.108   | 0.072   | 0.121   |
| 2.      | Telmisartan    | 0.021   | 0.052   | 0.039   | 0.077   |
| 3.      | Azelnidipine+ Telmisartan | 0.057   | 0.109   | 0.070   | 0.124   |
| 4.      | Azelnidipine + Microcrystalline cellulose (MCC) | 0.056   | 0.108   | 0.071   | 0.121   |
| 5.      | Azelnidipine+ Lactose (L) | 0.055   | 0.109   | 0.072   | 0.123   |
| 6.      | Azelnidipine+ Crospovidone (CP) | 0.056   | 0.109   | 0.072   | 0.121   |
| 7.      | Azelnidipine + Magnesium Stearate (MS) | 0.071   | 0.110   | 0.072   | 0.125   |
| 8.      | Telmisartan+ Microcrystalline cellulose (MCC) | 0.057   | 0.108   | 0.070   | 0.126   |
| 9.      | Telmisartan + Lactose (L) | 0.021   | 0.052   | 0.073   | 0.124   |
| 10.     | Telmisartan + Crospovidone (CP) | 0.022   | 0.052   | 0.071   | 0.123   |
| 11.     | Telmisartan + Magnesium Stearate (MS) | 0.024   | 0.049   | 0.072   | 0.122   |
| 12.     | Azelnidipine + Magnesium Stearate (MS) | 0.020   | 0.053   | 0.070   | 0.124   |
| 13.     | Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.021   | 0.054   | 0.071   | 0.121   |
| 14.     | Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS) | 0.022   | 0.053   | 0.072   | 0.123   |

Known Impurities of Azelnidipine (AZE 4, Azelnidipine (AZE) IMP A, AZE IMP A Acetoacetate) and Telmisartan (Telmisartan (TEL) IMP A, TEL IMP B) were detected, below the acceptance limits.

Table 7. Result of drug-excipient mixtures in terms of peak area counts at 30 ± 2°C/75 ± 5% RH & 40 ± 2°C/75 ± 5% RH after 04 weeks

| Sr. No. | Composition details | Drug-Excipient Ratio | Observation (Peak Area) | (% Difference in Peak Area) |
|---------|---------------------|----------------------|-------------------------|-----------------------------|
| 1.      | Azelnidipine        | ---                  | 525658                  | 535634                      |
| 2.      | Telmisartan         | ---                  | 2583251                 | 2546937                      |
| 3.      | Azelnidipine+ Telmisartan | 0.166:0.833 | 547550                  | 539769                      |
| 4.      | Azelnidipine + Microcrystalline cellulose (MCC) | 0.10:1.0 | 567868                  | 557584                      |
| 5.      | Azelnidipine+ Lactose (L) | 0.10:1.0 | 536690                  | 525796                      |
| 6.      | Azelnidipine+ Crospovidone (CP) | 0.1:1.0 | 529767                  | 515905                      |
| 7.      | Azelnidipine + Magnesium Stearate (MS) | 0.1:0.3 | 538064                  | 536746                      |
| 8.      | Telmisartan+ Microcrystalline cellulose (MCC) | 0.1:1.0 | 2649524                 | 2658468                      |
| 9.      | Telmisartan + Lactose (L) | 0.1:1.0 | 2597115                 | 2567489                      |
| 10.     | Telmisartan + Crospovidone (CP) | 0.1:1.0 | 2756875                 | 2698468                      |
| 11.     | Telmisartan + Magnesium Stearate (MS) | 0.1:0.3 | 2480810                 | 2479568                      |
| 12.     | Azelnidipine + (MCC) + (L) + (CP) + (MS) | 1:1 (Mixture of all excipients) | 592811                  | 595786                      |

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| Sr. No. | Composition details | Drug-Excipient Ratio | Observation (Peak Area) | (% Difference in Peak Area) |
|---------|---------------------|----------------------|-------------------------|---------------------------|
|         |                     |                      | Initial                  | 30 ± 2°C/75 ± 5% RH, after 04 weeks | 40 ± 2°C/75 ± 5% RH, after 04 weeks |
| 13.     | Telmisartan + (MCC) + (L) + (CP) + (MS) | 1:1 (Mixture of all excipients in equal proportion) | 2770197 | 2765697 | 0.16 | 2.91 |
| 14.     | Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS) | 1:1:1 (Mixture of all excipients in equal proportion) | 547284 | 546857 | 0.08 | 1.92 |

Table 8. Result of Drug-Excipient mixtures in terms of peak area counts at 60 ± 2°C, after 02 weeks

| Sr. No. | Composition details | Drug-Excipient Ratio | Observation (Peak Area) | (% Difference in Peak Area) |
|---------|---------------------|----------------------|-------------------------|---------------------------|
|         |                     |                      | Initial                  | 60 ± 2°C, after 02 weeks | 60 ± 2°C, after 02 weeks |
| 1.      | Azelnidipine        | ---                  | 526568                  | 536869 | -1.96 |
| 2.      | Telmisartan         | ---                  | 2583251                 | 2596985 | -0.25 |
| 3.      | Azelnidipine + Telmisartan | 0.166:0.833 | 547550 | 557858 | -1.88 |
| 4.      | Azelnidipine + Microcrystalline cellulose (MCC) | 01:10 | 567688 | 546748 | 3.69 |
| 5.      | Azelnidipine + Lactose (L) | 01:10 | 536690 | 546854 | -1.89 |
| 6.      | Azelnidipine + Crospovidone (CP) | 01:01 | 529767 | 538537 | -1.66 |
| 7.      | Azelnidipine + Magnesium Stearate (MS) | 01:00.3 | 538064 | 536548 | 0.28 |
| 8.      | Telmisartan + Microcrystalline cellulose (MCC) | 01:10 | 2649524 | 2579536 | 2.64 |
| 9.      | Telmisartan + Lactose (L) | 01:10 | 2597115 | 2479579 | 4.53 |
| 10.     | Telmisartan + Crospovidone (CP) | 01:01 | 2756875 | 2759654 | -0.10 |
| 11.     | Telmisartan + Magnesium Stearate (MS) | 01:00.3 | 2480810 | 2479596 | 0.05 |
| 12.     | Azelnidipine + (MCC) + (L) + (CP) + (MS) | 1:1 (Mixture of all excipients in equal proportion) | 592811 | 586854 | 1.00 |
| 13.     | Telmisartan + (MCC) + (L) + (CP) + (MS) | 1:1 (Mixture of all excipients in equal proportion) | 2770197 | 2697585 | 2.62 |
| 14.     | Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS) | 1:1:1 (Mixture of all excipients in equal proportion) | 547284 | 559547 | -2.96 |

The % difference in peak area counts was NMT 5%. Hence samples were found stable during Drug-Excipient studies at above mentioned conditions.
Fig. 3. Azelnidipine chromatogram

Fig. 4. Telmisartan chromatogram

Fig. 5. Azelnidipine + Telmisartan chromatogram

Fig. 6. Azelnidipine + (MCC) + (L) + (CP) + (MS) chromatogram
4. CONCLUSION

The physical and chemical stability of Drug-Excipient samples at different stability conditions, 30°C ± 2°C/75% ± 5% RH, 40°C ± 2°C/75% ± 5% RH for 04 weeks and at Temperature 60°C ± 2°C for two weeks were found satisfactory.

The binary mixtures which were tested at stability condition, did not changes any physical or chemical parameters. The colour, texture of the test samples remained same in side by side comparison with samples stored under ambient conditions. The analytical data of mixtures in the ratio of 2 gm (Drug: Excipient in 1:1 ratio) & 3 gm (Drug: Drug: Excipient in 1:1:1 ratio) did not show significant increase in the related substance from initial. Hence it is concluded that, all the excipients selected were compatible with the drug substance.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

Authors are thankful to M/s. Kimia Biosciences Limited, Gurugram, Haryana, for providing the necessary facility to carry out this experiment and the faculty of K. R. Mangalam University, Gurugram for their guidance.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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