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

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The Drug-Excipient compatibility testing was conducted at an early product development stage to determined 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 $30^0C \pm 2^0C/75\% \pm 5\%$ RH, $40^0C \pm 2^0C/ 75\% \pm 5\%$ RH for 04 weeks and another set of closed vials were stored in stability chamber at temperature $60^0C \pm 2^0C$ for 02 weeks.
Methodology: Samples were analyzed by validated RP-HPLC method using Inertsil C-18 Column 150 × 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.

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Keywords: Azelnidipine; Telmisartan; RP-HPLC; drug-excipient compatibility study; method validation.

1. INTRODUCTION

Drug-Excipient compatibility method was developed by which possible stability problems occurs 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 Pharmaceutical Limited, Haridwar, Uttrakhand. 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

100 mL. From this stock solution, 10 mL of solution was transferred in to 100 mL volumetric flask and the final volume was made up with diluent to got 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 $30^0C \pm 2^0C$/ 75% ± 5% RH, $40^0C \pm 2^0C$/ 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.

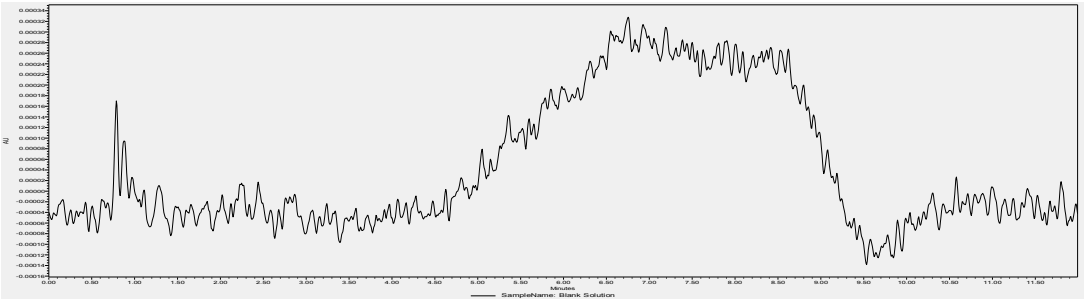

Fig. 1. Blank Chromatogram

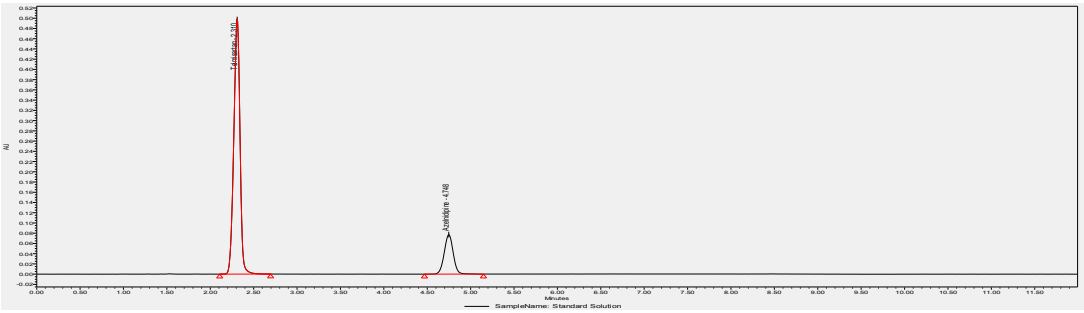

Fig. 2. Standard Solution Chromatogram

Table 2. Results of system suitability parameters

Injection	Telmisartan (A) & Azelnidipine(B) Standard sample									
	AREA		RT		USP Tailing Factor		USP Theoretical Plates		USP Resolution	
	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(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 3. Physical observations of drug-excipient compatibility (Pack Size 5.0 mL Glass Vial)

Sr. No.	Drug: Excipient	Physical Observations			
		Initial	$30^0C \pm 2^0C$ & RH 75% ± 5% (4 Weeks)	$40^0C \pm 2^0C$ & RH 75% ± 5% (4 Weeks)	$60^0C \pm 2^0C$ (2 Weeks)
1.	Azelnidipine	Complies	Complies	Complies	Complies
2.	Telmisartan	Complies	Complies	Complies	Complies
3.	Azelnidipine+ Telmisartan	Complies	Complies	Complies	Complies
4.	Azelnidipine + Microcrystalline cellulose (MCC)	Complies	Complies	Complies	Complies
5.	Azelnidipine+ Lactose (L)	Complies	Complies	Complies	Complies
6.	Azelnidipine+ Crospovidone (CP)	Complies	Complies	Complies	Complies
7.	Azelnidipine + Magnesium Stearate (MS)	Complies	Complies	Complies	Complies
8.	Telmisartan+ Microcrystalline cellulose (MCC)	Complies	Complies	Complies	Complies
9.	Telmisartan + Lactose (L)	Complies	Complies	Complies	Complies
10.	Telmisartan + Crospovidone (CP)	Complies	Complies	Complies	Complies
11.	Telmisartan + Magnesium Stearate (MS)	Complies	Complies	Complies	Complies
12.	Azelnidipine + (MCC) + (L) + (CP) + (MS)	Complies	Complies	Complies	Complies
13.	Telmisartan + (MCC) + (L) + (CP) + (MS)	Complies	Complies	Complies	Complies
14.	Azelnidipine + Telmisartan + (MCC) + (L) +(CP) + (MS)	Complies	Complies	Complies	Complies

Table 4. Chemical observations of drug-excipient compatibility at pack size 5.0 ml glass vial at long term stability (temperature $30^0C \pm 2^0C$ & RH 75% ± 5%)

Sr. No.	Drug: Excipient	Chemical Observations			
		Initial		$30^0C \pm 2^0C$ & 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 $40^0C \pm 2^0C$ & RH 75% ± 5%)

Sr. No.	Drug: Excipient	Chemical Observations			
		Initial		$40^0C \pm 2^0C$ & 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	0.065	0.115
14.	Azelnidipine + Telmisartan + (MCC) + (L) +(CP) + (MS)	0.022	0.053	0.066	0.116

Table 6. At temperature $60^0C \pm 2^0C$ (2 Weeks)

Sr. No.	Drug: Excipient	Chemical Observations			
		Initial		At Temperature $60^0C \pm 2^0C$ (2 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	0.072	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)	0.057	0.110	0.071	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 + (MCC) + (L) + (CP) + (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 INB 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)	
			Initial	30 ± 2°C/75 ± 5% RH, after 04 weeks	40 ± 2°C/75 ± 5% RH, after 04 weeks	30 ± 2°C/75 ± 5% RH, after 04 weeks	40 ± 2°C/75 ± 5% RH, after 04 weeks
1.	Azelnidipine	---	526568	525803	535634	0.15	-1.72
2.	Telmisartan	---	2583251	2576946	2548937	0.24	1.33
3.	Azelnidipine+ Telmisartan	0.166:0.833	547550	536936	537969	1.94	1.75
			2493446	2499208	2475735	-0.23	0.71
4.	Azelnidipine + Microcrystalline cellulose (MCC)	01:10	567688	568895	557584	-0.21	1.78
5.	Azelnidipine+ Lactose (L)	01:10	536690	537630	525795	-0.18	2.03
6.	Azelnidipine+ Crospovidone (CP)	01:01	529767	523795	515905	1.13	2.62
7.	Azelnidipine + Magnesium Stearate (MS)	01:00.3	538064	538064	536746	0.00	0.24
8.	Telmisartan+ Microcrystalline cellulose (MCC)	01:10	2649524	2668054	2658468	-0.70	-0.34
9.	Telmisartan + Lactose (L)	01:10	2597115	2584812	2567489	0.47	1.14
10.	Telmisartan + Crospovidone (CP)	01:01	2756875	2769745	2698468	-0.47	2.12
11.	Telmisartan + Magnesium Stearate (MS)	01:00.3	2480810	2468954	2479568	0.48	0.05
12.	Azelnidipine + (MCC) + (L) + (CP) + (MS)	1:1 (Mixture of all excipients	592811	585784	595786	1.19	-0.50

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	30 ± 2°C/75 ± 5% RH, after 04 weeks	40 ± 2°C/75 ± 5% RH, after 04 weeks
		in equal proportion)					
13.	Telmisartan + (MCC) + (L) + (CP) + (MS)	1:1 (Mixture of all excipients in equal proportion)	2770197	2765697	2689575	0.16	2.91
14.	Azelnidipine + Telmisartan + (MCC) + (L) +(CP) + (MS)	1:1:1 (Mixture of all excipients in equal proportion)	547284 2508225	546857 2578575	536755 2574848	0.08 -2.80	1.92 -2.66

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	2589685	-0.25
3.	Azelnidipine+ Telmisartan	0.166:0.833	547550 2493446	557858 2467046	-1.88 1.06
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 2508225	558547 2579648	-2.06 -2.85

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

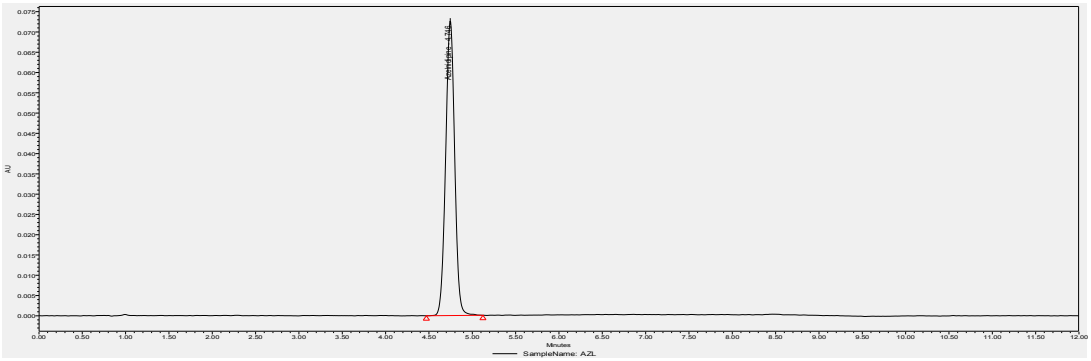

Fig. 3. Azelnidipine chromatogram

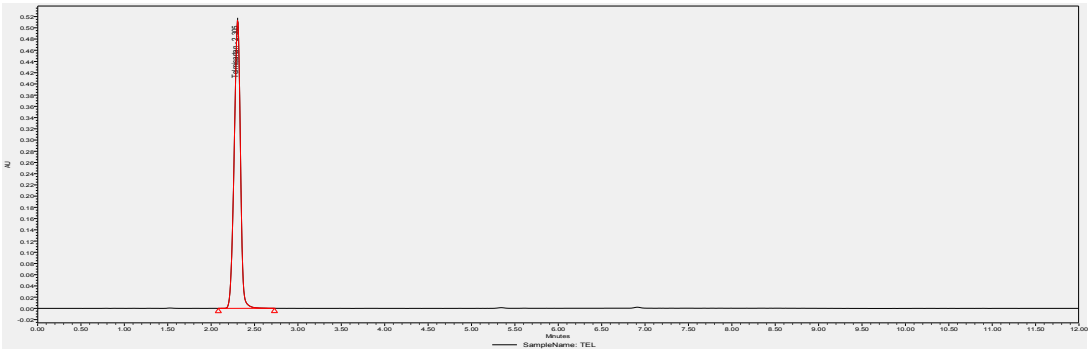

Fig. 4. Telmisartan chromatogram

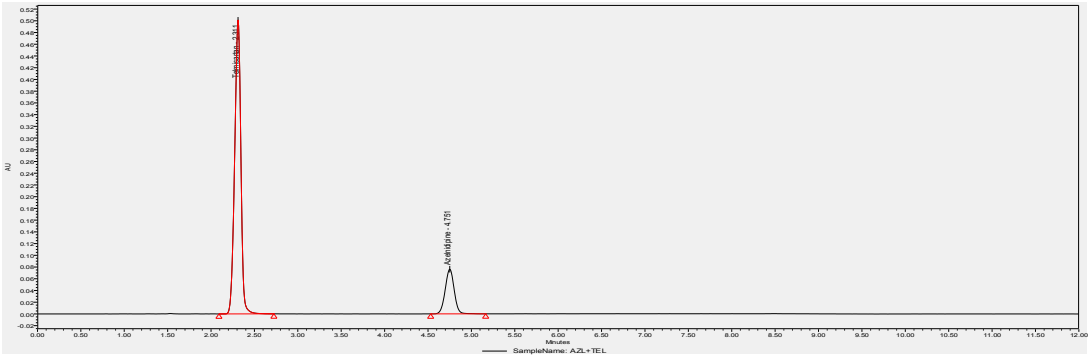

Fig. 5. Azelnidipine + Telmisartan chromatogram

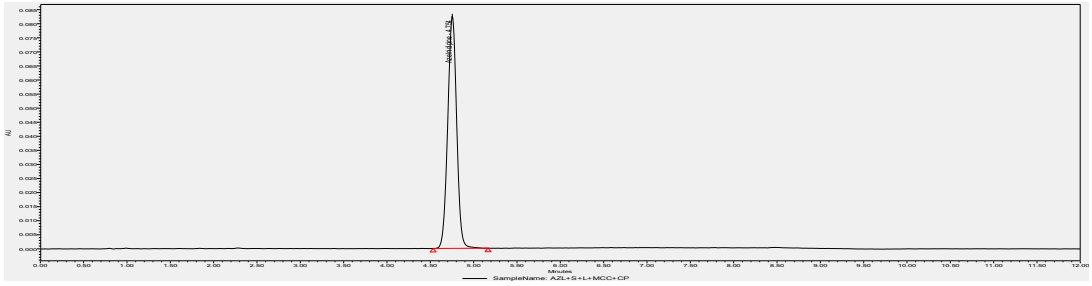

Fig. 6. Azelnidipine + (MCC) + (L) + (CP) + (MS) chromatogram

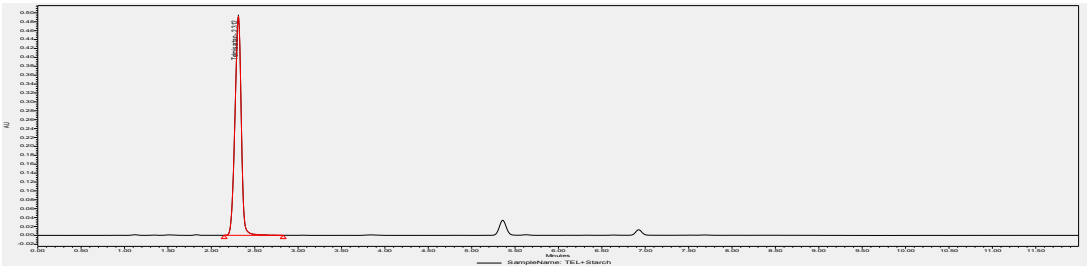

Fig. 7. Telmisartan + (MCC) + (L) + (CP) + (MS) Chromatogram

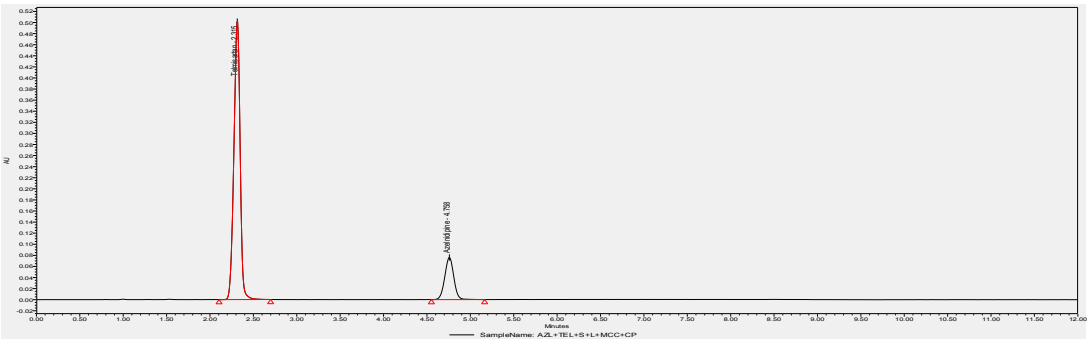

Fig. 8. Azelnidipine + Telmisartan + (MCC) + (L) + (CP) + (MS)

4. CONCLUSION

The physical and chemical stability of Drug-Excipient samples at different stability conditions, $30^0C \pm 2^0C/75\% \pm 5\%$ RH, $40^0C \pm 2^0C/75\% \pm 5\%$ RH for 04 weeks and at Temperature $60^0C \pm 2^0C$ 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.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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