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Synthesis and Quantitation of Process-Related Impurity in Felodipine Bulk and Formulation

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ABSTRACT

This research is directed towards Synthesis and quantitation of process-related impurity in Felodipine bulk and formulation. The synthesis of 1,4-Dihydro-2,6-Dimethyl-4-(m- chloro phenyl) pyridine-3,5 Dicarboxylate was identified, characterized, developed and validate by using various analytical techniques such as UV, IR, NMR for the assessment of impurities in the bulk and formulation in Felodipine. The synthesis of of 1,4-Dihydro-2,6-Dimethyl-4-(m- chloro phenyl) pyridine-3,5 Dicarboxylate was performed by Hantzch pyridine synthesis, by using m-chlorobenzaldehyde, ethylacetoacetate, in presence of ammonia and methanol as a catalyst. The percentage yield was observed to be 80.29%. The preliminary evaluation was performed via melting point, elemental analysis and thin layer chromatography (TLC). Melting point of obtained synthesised compound was noticed to be 134-137^{0}C, whereas Rate of flow (Rf) value was estimated and found to be 0.70. The TLC of impurity was performed by using Benzene and Methanol (6:1). The structure confirmation of obtained synthesized impurity by using sophisticated analytical instrument viz, Fourier transform infra red(FT-IR), nuclear magnetic resonance (NMR) and ultra violet (UV) spectroscopy. The method was validated as per ICH guidelines and was found to be linear, precise, robust, accurate, rugged.

Keywords: Impurity, Felodipine, UV, Validation.

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INTRODUCTION

Felodipine is chemically known as of Ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate. Felodipine is under the class of calcium channel blocker. Its molecular formula is $C_{18}H_{19}Cl_2NO_4$.

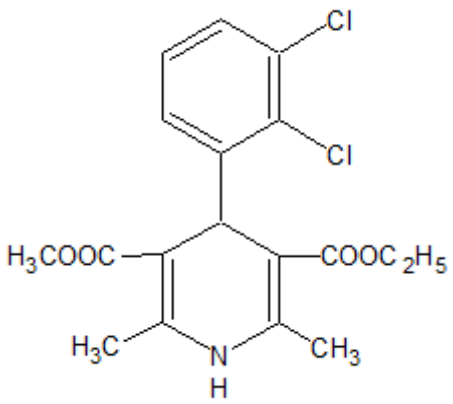


Figure 1: Chemical structure of Felodipine

Felodipine is a slightly yellowish, crystalline powder. The molecular weight of felodipine 384.26. Felodipine is a part of the dihydropyridine class of calcium channel antagonists. It reversibly compete with calcium channel blockers for dihydropyridine binding sites, blocks calcium dependent Ca^{++} currents in vascular smooth muscle. The use of felodipine to treatment for hypertension, lower the blood pressure.

MATERIALS AND METHOD

Chemicals (AR- Analytical Grade reagents)

Ethylacetoacetate (AR), m-chlorobenzaldehyde (AR), methanol (AR), ammonia (AR) .

Instruments Ft-Ir

The IR spectra were recorded for the structural elucidation of impurities by KBr press pellet technique.

UV-Visible spectrophotometer

The wavelength of FI was found to be 237 nm. Synthesis, characterization and determination by using UV-Visible spectrophotometer (UV-1650 PC) SHIMADZU INC.

NMR

$CDCl_3$ solvent.

Experimental

The synthesis of FI was carried out by Hantzch synthesis process. In this procedure using 0.01 mole of m-chlorobenzaldehyde, 0.02 mole of ethylacetoacetate, in presence 0.01 mole of ammonia

and 10 times of methanol as catalyst. The mixture was reflux for 8 hours and poured in ice-cold water. The precipitated compound was filtered and purified by recrystallization using methanol.

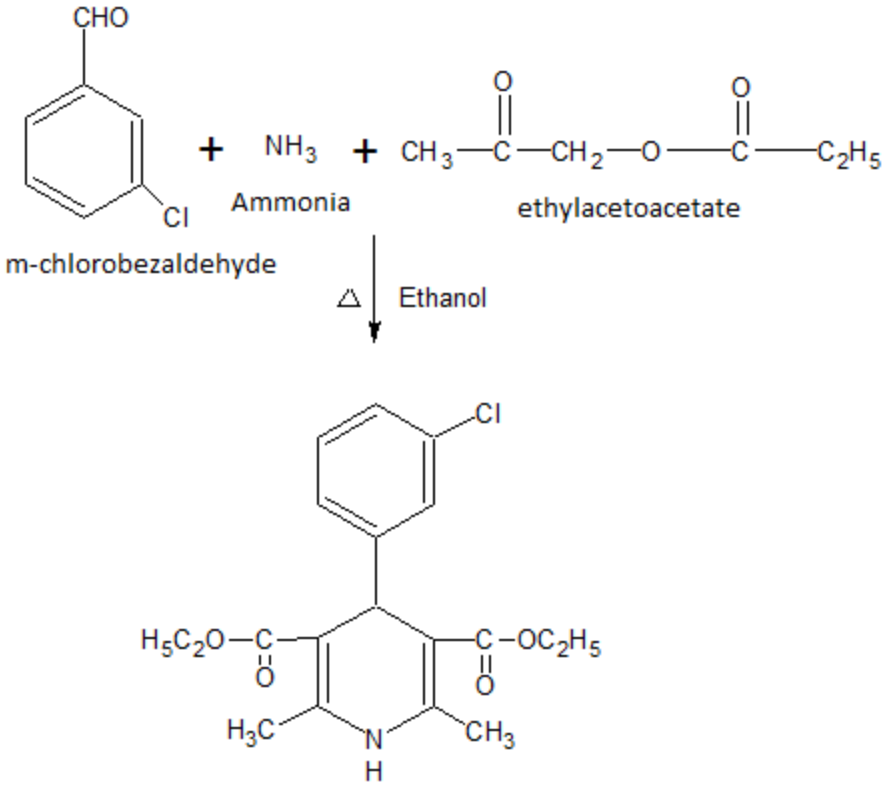


Figure 2: Scheme for the Synthesis of FI.

RESULTS AND DISCUSSION

Table 1: Physiochemical properties

Molecular formula	Molecular weight	M.P ^{o}C	Rf value	% yield
$C_{19}H_{22}ClNO_4$	363.5	134-137	0.70	80.29%

IR Data[5]

The major functional groups are primary amine, chloro and carbonyl groups. Obtained peaks in IR spectrum are as follows,

IR (KBr) cm^{-1}: 3323.46 (NH- Stretch), 2980.12-3097.78 (C-H Aromatic Stretch), 2783 (C-H Aliphatic Stretch), 1701.27 (C=O), 1489.10 (C=C), 1375.29 (CH_3 Bend), 1172.76-1215.19 (C-O-C Stretch), 873.78 (CH out of plane bending of meta-benzoid), (Substitution at meta position of benzene ring).

NMR Data[4,5]

C NMR (CDCl3) [13]

δ=14.15 (2C,CH_3 Carbon attached to $CH_{2),}$50.98 (2C,CH_2 Carbon attached to CH_3), 167.43 (2C, Carbonyl carbon attached to 1,4-dihydropyridine ring), 19.36 (2C,CH_3 Carbon attached to 1,4-dihydropyridine ring), 128.13 (2C,C=C of 1,4-dihydropyridine ring), 128.97(2C,C=C of 1,4-dihydropyridine ring), 39.38 (1C, Carbon attached to 1,4-dihydropyridine ring), 144.44 (6 Carbon of phenyl ring).

H NMR (CDCl3) [1]

δ= 5.49 (1H,NH of 1,4 dihydropyridine), 1.25 (6H,CH_3 of 1,4 dihydropyridine), 4.35 (4H, CH_2 proton of ester), 3.91 (6H,CH_3 proton of ester), 5.49 (1H,CH attached to 1,4 dihydropyridine), 7.124 (2H,CH attached to chlorobenzene ring), 7.188 (2H,CH attached to chlorobenzene ring).

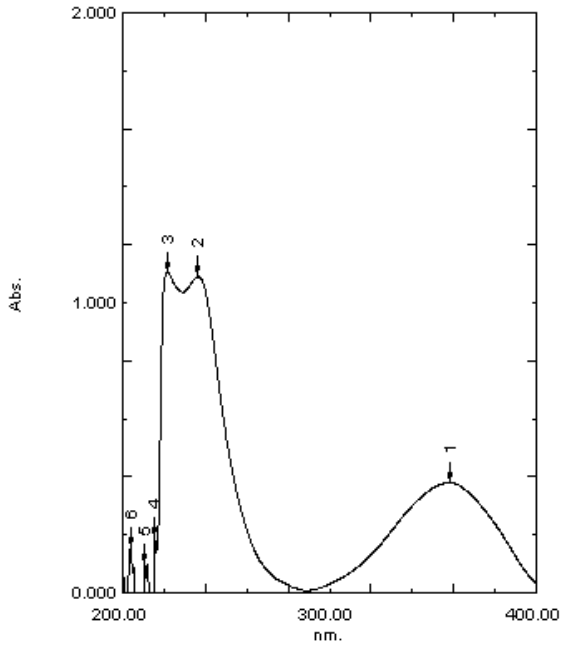
GC-MS Data[10]

Gas Chromatogram of FI shows a single peak at 25.63 min. which indicates purity of synthesized FI. Mass spectrum at 25.63 min was recorded. Peak appear at 365 indicates presence of molecular ion peak. Major base peak at 252 shows 100% abundance.

UV Spectrum[9]

The λmax of FI in methanol was found to be 234 nm (1) n-π^* transitions. Another peak appears at 360 nm (2) π-π^* transitions.

UV method development



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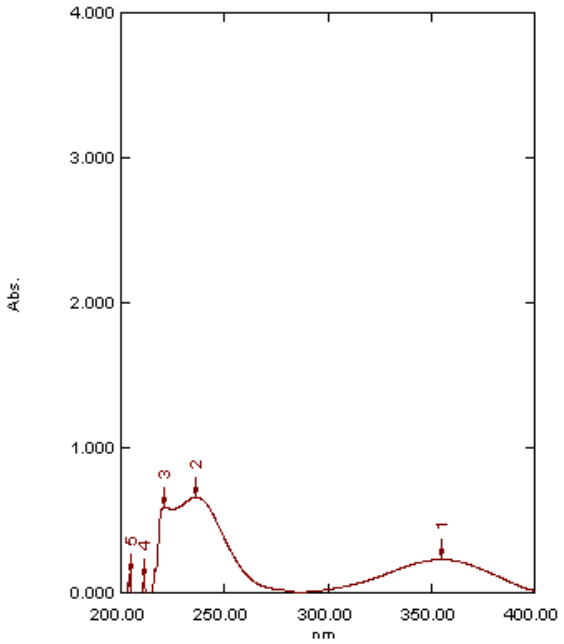

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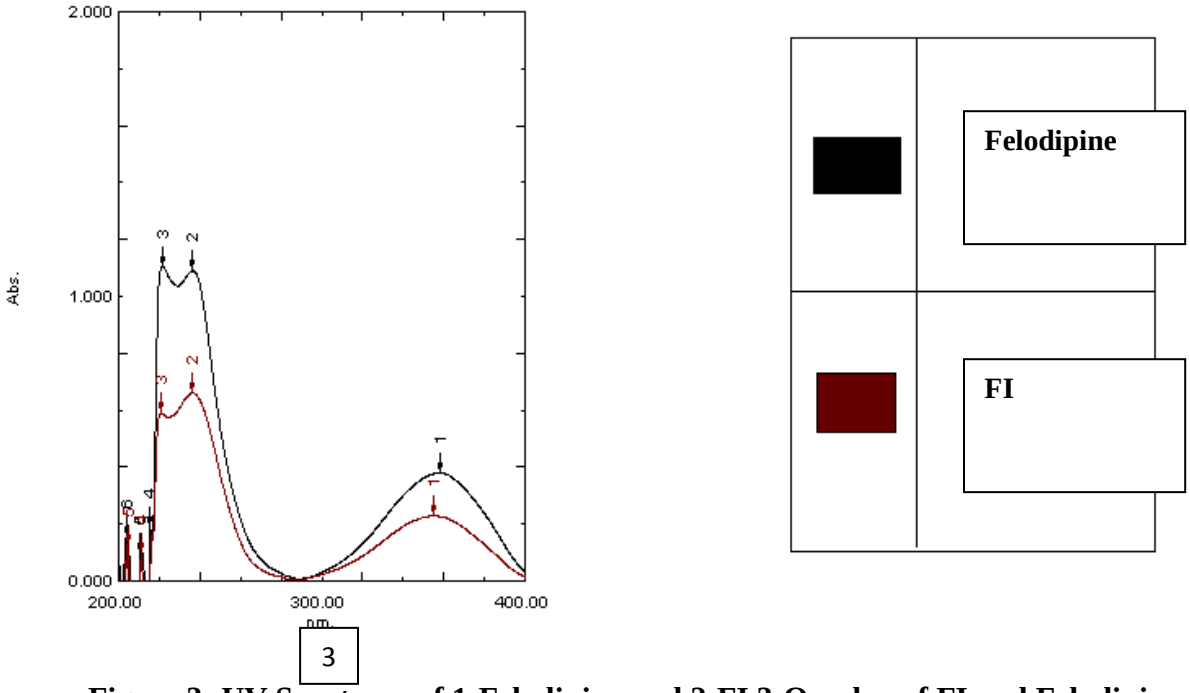

Figure 3: UV Spectrum of 1-Felodipine and 2-FI 3-Overlay of FI and Felodipine

Study of linearity

Different volumes 2, 4, 6, 8, 10, 12, 14, 16, 18 of FI standard stock were transferred to six separate 10 ml glass volumetric flask and volume were made up to the mark with methanol to obtain series of concentration in the range 2-18µg/ml. The absorbance of solution were recorded at 237nm. The regression coefficient was found to be 0.996 and slope was found to be 0.047.

Table 2: Linearity

Sr. no	Concentration (ppm)	Absorbance
1	2	0.1198
2	4	0.1948
3	6	0.3173
4	8	0.4044
5	10	0.4873
6	12	0.5720
7	14	0.6896
8	16	0.7833
9	18	0.8755

Precision

Precision is defined as the variability among replicate measurements. The developed method was found to be precise as the %RSD values for the repeatability (intraday) and intermediate precision (inter-day) studies were below 2% respectively.

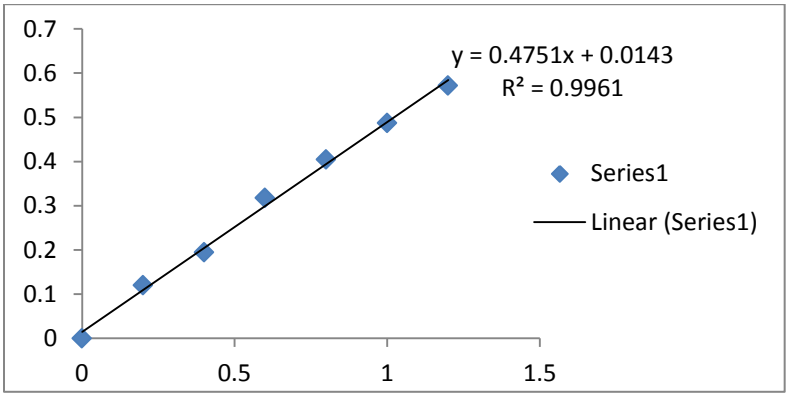

Figure 4: Calibration curve

Table 3: Intra-day Precision

Sr. No	Concentration (ppm)	Absorbance	SD	%RSD
1	6	0.2897	0.0043	1.49
2	6	0.2869		
3	6	0.2877		
4	6	0.2971		
5	6	0.2911		
6	6	0.2833		
7	6	0.2914		

Table 4: Inter-day Precision

Sr. No	Concentration (ppm)	Absorbance	SD	%RSD
1	6	0.3367	0.0047	0.01406
2	6	0.3324		
3	6	0.3419		
4	6	0.3444		
5	6	0.3351		
6	6	0.3316		
7	6	0.3378		

Ruggedness

The ruggedness of developed method was checked by analyzing FI by different analysts at similar operational and environmental conditions. The % RSD values were found to be less than 2%.

Table 5: Ruggedness

Sr. No	Concentration (ppm)	Absorbance 1	Absorbance 11	SD 1	SD 11	%RSD 1	%RSD 11
1	6	0.2816	0.2916	0.004413	0.0055	1.55	1.94
2	6	0.2843	0.2839				
3	6	0.2711	0.2812				
4	6	0.2833	0.2844				
5	6	0.2812	0.2811				
6	6	0.2916	0.2952				
7	6	0.2952	0.2855				

Robustness

Robustness was performed by slightly changing wavelength the method found robust with % SD 0.002364 and % RSD 0.833.

Table 6: Robustness

Sr. No	Concentration (ppm)	Absorbance 1	Absorbance 11	SD 1	SD 11	%RSD 1	%RSD 11
1	6	0.2877	0.2866	0.002364	0.00473	0.833	1.65
2	6	0.2852	0.2812				
3	6	0.2844	0.2865				
4	6	0.2811	0.2915				
5	6	0.2843	0.2846				
6	6	0.2812	0.2951				
7	6	0.2825	0.2915				

Accuracy and Recovery

The results within the range 97.00 - 100.00 ensure an accurate method.

Table 7: Recovery

Sr. No	Drug / Formulation	Percentage recovery			Mean	SD	%RSD
		50%	100%	150%			
1	Bulk	99.23	99.55	99.73	97.93	1.95	1.99
2	Tablet	99.79	97.66	98.87	98.77	1.06	1.08

LOD and LOQ

LOD 0.0211 and LOQ 0.07301 and used to decide method was selective and sensitive.

CONCLUSION

The synthesis of process related impurity of Felodipine carried out Hantzch pyridine synthesis method. The impurity of Felodipine in bulk and formulation was synthesized, characterized by UV-spectrophotometric method was developed according to ICH Q2B guidelines for FI from felodipine bulk and tablet formulation. On the basis spectral data, the structure of impurity was characterized as 1,4-Dihydro-2,6-Dimethyl-4-(m- chloro phenyl) pyridine-3,5 Dicarboxylate. The structure conformation of impurity was done by IR, UV, NMR, GC-MS analytical method. The method was found linear, precise, accurate, robust, rugged.

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