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Validated HPLC Method for Stability-Indicating Quantitative Determination of L-Carnitine in Pharmaceuticals and Supplements

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Abstract: The study created a new stability-indicating reverse-phase high-pressure liquid chromatographic (RP-HPLC) method to measure the amount of L-carnitine in bulk and pharmaceutical dosage forms. Analytical performance parameters-system suitability (RSD = 0.14%; TP = 4696; TF = 1.36), assay (method precision = 99.68%; intermediate precision = 99.39%), accuracy (99.78%), specificity (both standard and sample are passed), stability (within ±2% of the standard), robustness, etc.-were determined according to ICH guidelines. The detection (LOD) and quantitation (LOQ) limits were 21 and 64 µg/ml, respectively. Percent recovery in the accuracy study was within the limit of 98 to 102%, which proved the method was validated for food supplements. However, the process was simple, precise, accurate, robust, and rapid, making it suitable for quantifying L-carnitine in pharmaceutical products and food supplements.

Keywords: Reverse Phase HPLC, L-carnitine, Method development and validation, ICH Guidelines, Pharmaceuticals and supplements.

1. Introduction

L-carnitine (Figure 1) ((R)-3-carboxy-2-hydroxy-*N*,*N*,*N*-trimethyl-1-propaminium hydroxide inner salt) is a vitamin-like amino acid derivative, which is an essential factor in fatty acid metabolism as an acyltransferase cofactor and in energy production processes [1]. Insufficient L-carnitine causes fat to build up in the cytosol and disrupts energy generation from long-chain fatty acids, particularly during fasting or physiological stress [2]. L-carnitine is available in various pharmaceutical forms, such as injections, syrups, tablets, and capsules, which treat primary and secondary carnitine deficiencies and conditions like dyslipoproteinemia and Alzheimer's disease [3].

L-carnitine is crucial in cellular metabolism, particularly in transporting long-chain fatty acids into mitochondria for β-oxidation. Analyzing its biological functions comes with several analytical challenges, mainly due to its chemical nature, physiological distribution, and interactions [4]. L-carnitine levels can be very low in specific biological matrices (like cerebrospinal fluid or some cell types), requiring highly sensitive analytical methods (e.g., LC-MS/MS) for sample preparation and enrichment without losing the analyte. L-carnitine is structurally similar to acylcarnitines, choline, and other quaternary amines. This isn't easy to separate using standard chromatographic methods, requiring high-resolution chromatography or tandem MS for precise identification and quantification [5,6]. Being a zwitterion with high polarity, L-carnitine can be tricky to ionize efficiently and can lead to poor sensitivity and signal suppression in electrospray ionization (ESI) for optimization of ion source conditions and mobile phase composition. Biological matrices like plasma, urine, or tissue extracts introduce interference that can affect recovery, accuracy, and reproducibility, requiring extensive method validation and stable isotope-labeled internal standards [7]. Carnitine appears safe but may not be very helpful for other diseases, such as reducing fatigue or enhancing athletic performance [8]. Through forming a long-chain acetylcarnitine ester and its transportation by carnitine palmitoyltransferase, carnitine plays a role in the movement of fatty acids across the mitochondrial membrane [9,10]. L-carnitine and its esters can degrade or convert during storage or sample processing,

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affecting the risk of physiological levels' misinterpretation. This analytical challenge indicates the strict control of sample storage (cold, low pH), quick processing, and use of preservatives [11-13].

Earlier methods used to study L-carnitine's biological functions focused more on biochemical assays, radiolabeling, and tissue distribution studies, especially before the advancement of modern analytical tools like LC-MS/MS. For early metabolic profiling, carnitine and associated metabolites are separated on paper or silica gel plates using thin-layer chromatography (TLC) and paper methods. However, the quantification of carnitine/acylcarnitines is poor due to its low resolution and sensitivity [14]. Early HPLC methods approached reversed-phase or ion-pair HPLC with UV detection. More specific quantification of L-carnitine in biological samples required derivatization for UV detection (due to lack of chromophores) and limited ability to detect low concentrations or differentiate isomers [15]. An extensive literature review indicates that only a limited number of analytical methods have been reported for determining L-carnitine in pharmaceutical products [16,17]. The United States Pharmacopeia (USP) outlines two HPLC methods for quantifying L-carnitine in oral solutions and tablet formulations [18-20]. An aminopropylsilane-bonded silica gel column and detection at 205 nm are used in the tablet approach. This column is uncommon and needs special precautions to be maintained. In addition, this method requires a prolonged equilibration of the column (3 h), which is therefore time-consuming for industrial purposes [21-23]. Other reported methods for quantification of l-carnitine in tablets are limited in either low sensitivity for dissolution testing or not being stability-indicating, where some of the methods only mentioned the phosphate buffer without the name and amount of the reagent to prepare the buffer solution [24].

Considering ICH guidelines, the present study describes a simple, validated, and stability-indicating analytical method for determining tablet L-carnitine. This work aims to provide a straightforward, precise, and accurate RP-HPLC method for estimating L-carnitine in prescription dose forms and bulk. According to ICH requirements, a new RP-HPLC method is established in this study for the measurement of L-carnitine in pharmaceutical formulations, and it shows excellent economy, sensitivity, and reproducibility.

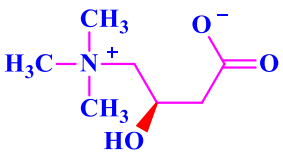

Figure 1. The chemical structure of L-carnitine.

2. Materials and Methods

2.1 Instrument and Chromatographic Conditions

This technique utilized the Shimadzu HPLC 2050 liquid chromatographic system, which included a PDA detector and an autosampler. Chromatographic separation was achieved on a GL Science C18 column (150 x 4.6 mm, 5 µ particle size) with mobile buffer (pH 2.5) and methanol (70:30 v/v) at 40°C column temperature. The flow rate was 0.75 ml/min, and the detector wavelength was kept at 220 nm to monitor elution. The injection volume was 50 µL, and the total run time was 12 min.

2.2 Reagents and Solutions

Radiant Pharmaceuticals, Dhaka, Bangladesh, kindly provided pure samples, working standards, and placebos of L-carnitine. The methanol, purified water & all other reagents used in this study were of HPLC grade supplied by Radiant Pharmaceuticals Ltd.

2.3 Mobile Phase Preparation

Buffer: 1.01 grams of 1-heptanesulfonic acid sodium salt and 2.40 grams of sodium dihydrogen phosphate dissolved into 1000 ml of purified water and adjusted pH to 2.5 with dilute phosphoric acid solution. The mobile phase was a mixture of buffer (pH 2.5) and methanol (70:30% v/v) which was filtered through a 0.45 mm membrane filter under vacuum filtration.
Why the chosen conditions (pH 2.5, 220 nm): Since the pKa of L-carnitine is 3.8, we tried to keep the pH of the mobile phase in acidic conditions to stabilize the sample in the mobile phase for a long time. Although L-carnitine shows maximum absorption at around 205 nm, stabilizing the system takes a long time. As a result, 220 nm is selected for L-carnitine, and the baseline of the peak is also better at 220 nm than at 205 nm.

2.4 Preparation of Diluent

In diluent preparation, no buffer is needed; purified water and methanol are needed to prepare the mobile phase. Water and methanol were mixed at a ratio of 95:5.

2.5 Preparation of Standard Solution

200 mg of L-carnitine working standard was weighed and transferred to a 100-mL volumetric flask containing 70 mL of diluent. The solution was kept for sonication for 10 min and cooled to room temperature. The final volume of the stock solution was made up to the mark with the diluent. Furthermore, 5 ml of this solution can be transferred to a 20 ml volumetric solution and filled to the mark with a diluent. The final concentration is represented as 500 µg/ml. Pass the solution through a nylon disc filter having 0.45 µm or finer porosity.

2.6 Preparation of Sample Solution (Assay):
Ten tablets, each containing 750 mg of L-carnitine, were weighed; the average weight was calculated, the sample was crushed, and the sample powder equivalent to 500 mg of L-carnitine was accurately weighed and transferred to a 250 ml volumetric flask with 200 ml of diluent and shaken for 15 minutes in a mechanical shaker. The solution was kept for sonication for 10 min with intermittent shaking and kept at room temperature. The final volume of the stock solution was made up to the mark with the diluent. The sample was centrifuged at 4000 rpm for 10 minutes. A 5 ml supernatant sample was taken into a 20 ml volumetric solution and volume up to the mark with diluent. The solution passed through a nylon disc filter with 0.45 µm or finer porosity.

3 Method Development

A range of mobile phases was examined to create a stability-indicating RP-HPLC method for measuring L-carnitine in tablet dosage form. The suitability of the mobile phase was assessed using the assay's selectivity and sensitivity.

4 Method Validation

Once the HPLC method development was over, the method was validated in terms of parameters like system suitability, specificity, precision, accuracy, linearity and range, LOD, LOQ, ruggedness, robustness, stability, etc. Values for the percentage relative standard deviation were computed for every parameter. ICH regulations validated the suggested HPLC method.

5 System Suitability

To confirm the system's performance, system suitability parameters were examined. Five replicate samples containing L-carnitine (500 µg/ml) were analyzed using the developed method. When the system's applicability was evaluated, variables such as retention duration, percent relative standard deviation (% RSD) of peak area, theoretical plate count, and tailing factor were considered. The developed method has produced a theoretical plate above 2000 for L-carnitine with a tailing factor of less than 2. Similarly, the percent relative standard deviation (% RSD) of peak area and retention time was less than 2, ensuring the developed method's suitability. Results are shown in Table 1.

Table 1. System suitability conditions of the developed method.

Test Parameters	Observation	Specification	Result (Pass/Fail)
%RSD of the area of 5 replicate injections of Standard Solution	0.14	≤ 2.00	Pass
Theoretical Plate Count	4696	NLT 2000	Pass
Tailing Factor	1.36	NMT 2.0	Pass

Table 2. Method precision and intermediate precision for Assay (%) determination.

Precision of L-carnitine (% of Assay)		
Sample ID	**Method Precision (%)**	**Intermediate precision (%)**
Sample-1	99.00	99.65
Sample-2	99.07	98.62
Sample-3	99.61	99.79
Sample-4	101.58	98.90
Sample-5	99.01	99.88
Sample-6	99.82	99.39
Average	99.68	99.39
STDEV	0.99	0.51
%RSD	0.99	0.51
Average of 12 samples: 99.53		
STDEV of 12 sample: 0.77		
% RSD of 12 samples: 0.77		

6. Method Precision

Six independent sample preparations of a single formulation lot were used to assess precision. The sample preparation instructions were followed to prepare the sample solution. The percentage relative standard deviation (% RSD) was less than 2% for the method, proving that the technique is precise. Results are shown in Table 2.

6.1 Intermediate Precision

Another analyst carried out the intermediate method precision on another day using another column and instruments. The standard and six sample solutions were prepared by following the standard and sample preparation. The result of the RSD of six samples was found to be less than 2.0%. Results are shown in Table 2.

7. Accuracy

The method's accuracy was determined by interpolating replicate (n = 3) peak areas of three accuracy standards (300, 500, and 700 µg/ml). The percentage of recovery was computed for every instance. The mean % recoveries obtained were 100.01, 99.81, and 99.78% for 60, 100, and 140% concentration levels, respectively. The range of 99.57–101.05 percent for the mean recoveries indicates no interference from excipients. The outcomes appear in Table 3.

Table 3. Summary of accuracy findings.

Accuracy Level	Sample ID	% of recovery	Average (%)	SD	% RSD	Average (%)	% RSD
60 %	Sample 1	99.67	100.01	0.67	0.67	99.78	0.15
	Sample 2	100.78					
	Sample 3	100.57					
100%	Sample 1	99.80	99.81	0.04	0.04		
	Sample 2	99.77					
	Sample 3	99.85					
140%	Sample 1	99.92	99.78	0.14	0.14		
	Sample 2	99.78					
	Sample 3	99.63					

8. Linearity

The calibration curve constructed for L-carnitine was linear over the concentration range of 300-700 µg/ml. Peak areas of L-carnitine were plotted versus its concentration, and linear regression analysis was performed on the resultant curve. The correlation coefficients of R^2 = 1.000 prove linear regression analysis. The regression equation is Y = mx + c, where x is the concentration (µg/mL). Typically, the regression equation for the calibration curve was found to be y = 681.294x - 338.600, where the determination coefficient of the calibration curve, R^2 = 1.000. The linearity curve is shown in Figure 2, and the linearity results are shown in Table 4.

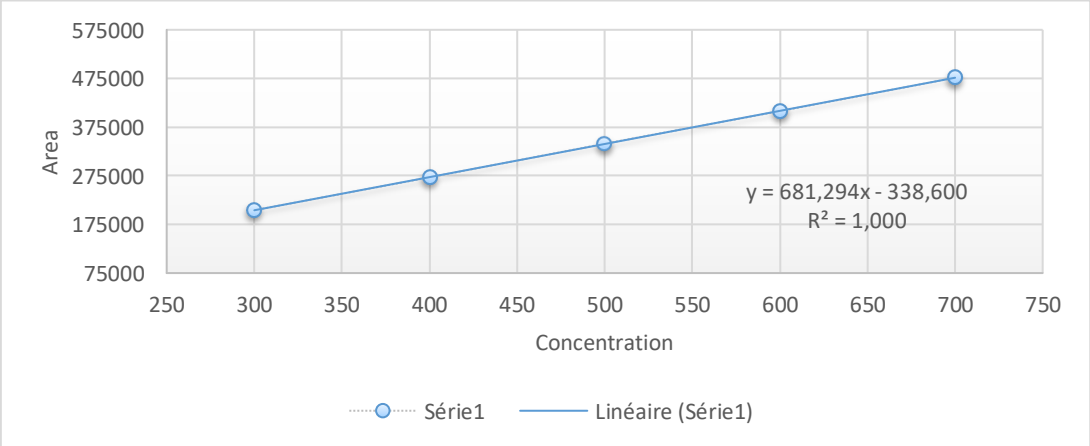

Figure 2. Linearity Curve (Concentration versus Area: R^2 = 1.000).

Table 4. Linearity result of L-carnitine.

Concentration (µg/ml)	Area
300	204076
400	272188
500	340118
600	408686
700	476474

9. Specificity

The condition of the HPLC method, like the percentage of organic solvent in the mobile phase, pH of buffer flow rate, etc., was changed. Despite the modifications above, shift retention times and slight alterations in peak forms were observed, but no new peaks were discovered. Retention time and placebo interference are given in Table 5. Peaks of diluent, placebo, standard, and sample solutions are shown separately from Figures 3-6.

Table 5. Specificity result of L-carnitine.

Sample ID	Observation	
	Retention Time	Remarks
Diluent	No interfere	No diluent Peak
Placebo	No interfere	No Placebo Interference
Standard	3.56	Passed
Sample	3.54	Passed

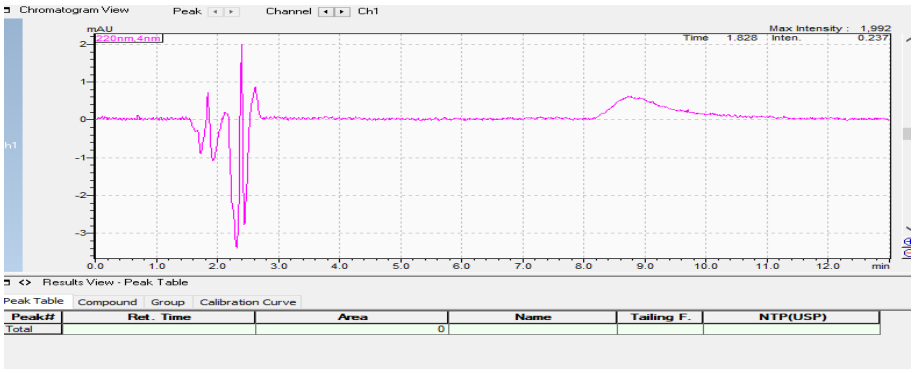

Figure 3. The chromatogram of blank solution for L-carnitine.

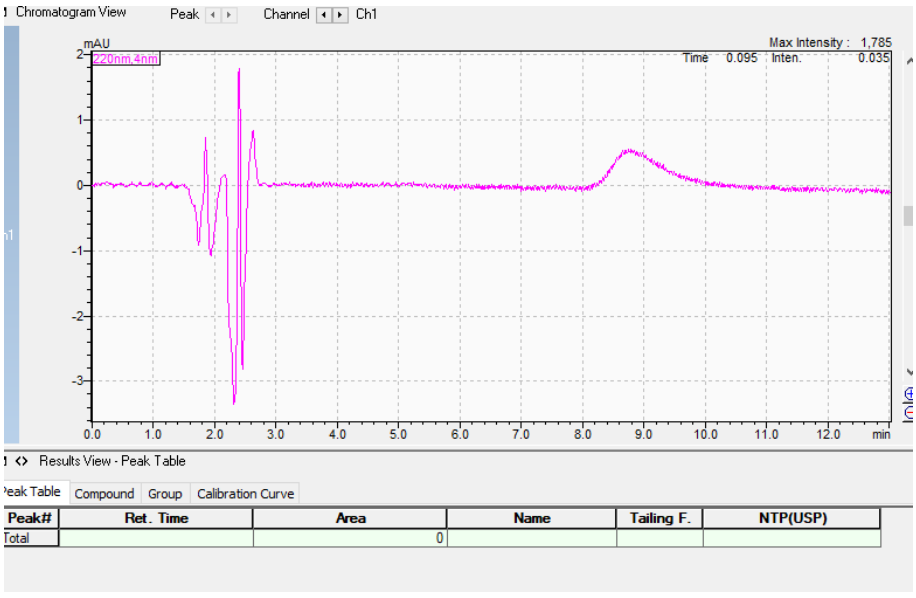

Figure 4. The chromatogram of placebo solution for L-carnitine.

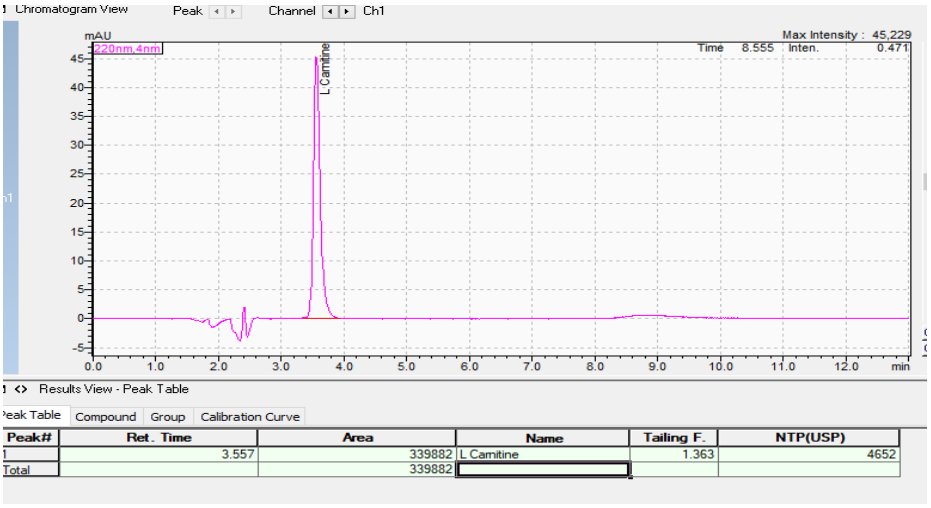

Figure 5. The chromatogram of standard solution for L-carnitine.

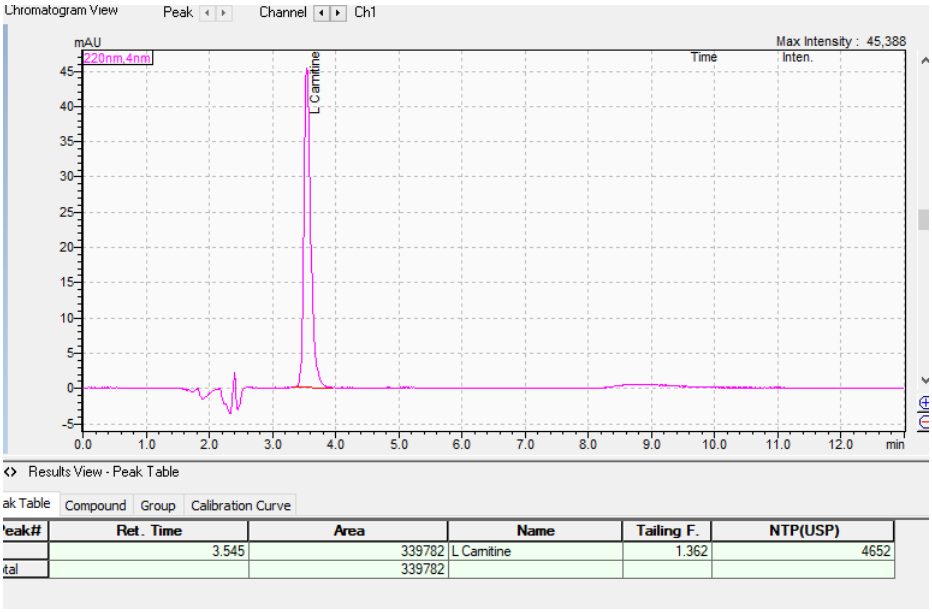

Figure 6. The chromatogram of sample solution for L-carnitine.

Table 6. Solution stability for standard and sample solution of L-carnitine.

Time Point (hour)	Standard Solution (Peak Area)	% Deviation	Sample Solution (Peak Area)	% Deviation
0	339882	Not applicable	341257	Not applicable
4th hour	340124	-0.07	340529	0.21
8th hour	337234	0.78	346875	-0.47
12th hour	341245	-0.40	339914	0.39
16th hour	336324	1.05	342574	-1.27
20th hour	339541	0.10	338424	0.83
24th hour	338964	0.27	342678	0.42

10. Sensitivity

The standard deviation and slope of the calibration curve were used to determine the sensitivity of the suggested approach in terms of LOD (limit of detection) and LOQ (limit of quantification).

The LOD and LOQ were determined by using the flowing equation:

LOD: 3.3 x σ/S

LOQ: 10 x σ/S
σ = Average standard deviation
S = slope of the curve
LOD: 21 (µg/ml)
LOQ: 64 (µg/ml)

11. Solution Stability

This study shows that when the standard and sample vials are stored in the sample tray in HPLC, they remain stable at 15 °C. The assay value did not significantly change, and the findings were within ±2% of the standard. Table 6 displays the stability study results.

12. Robustness

Minor but intentional adjustments to the technique parameters did not negatively impact the method's performance, indicating that the approach was robust. As expected, the retention time of analytes decreased with increasing mobile phase flow rate and vice versa. A slight decrease in the retention time of the analytes was observed with increasing column oven temperature. While standards and samples were often evaluated simultaneously and at the same flow rate and temperature for routine quality control analysis, flow rate and temperature had no adverse effects on the procedure. The results of robustness are shown in Table 7.

Table 7. Robustness test of L-carnitine.

Robustness Parameter	Variation	Retention time	Assay (%)	USP Plate Count	USP Tailing
Flow rate	0.65 ml/min	4.03	99.06	4405	1.35
	0.75 ml/min	3.55	99.64	4578	1.32
	0.85 ml/min	3.11	100.35	4623	1.41
Column Temperature	38°C	3.59	100.51	4539	1.29
	40°C	3.55	99.64	4578	1.32
	42°C	3.42	100.05	4520	1.33
Mobile Phase composition	Buffer: MeOH (22:78)	3.05	99.87	4635	1.45
	Buffer: MeOH (27: 73)	3.55	99.64	4578	1.32
	Buffer: MeOH (32:68)	3.97	100.11	4610	1.30

13. Application of Validated Method for Assay of L-carnitine in Pharmaceutical Dosage Form as well as in Food supplement

The developed method was successfully implemented in the assay of L-carnitine in pharmaceutical dosage form and food supplements, in which the assay result was found to be 99.53%. According to ICH Q2R1 criteria, the technique validation results were good.

The peak areas were linear over the concentration range of 300-700 µg/ml with a correlation coefficient of 1.000. Method specificity can be proved using the "peak purity" parameter in the 'Lab solution' software of HPLC. The medicine in the blend's unaffected assay verifies that no excipients are interfering. The difference between method precision and intermediate precision was less than 2%. Percent recovery in the accuracy study was within the 98 to 102% limit.

Conclusive Remarks

In this investigation, an isocratic liquid chromatographic method has been described and validated for the qualitative and quantitative determination of L-carnitine in bulk and its formulation. The method showed acceptable assay precision (<2% RSD), and the mean % recovery (99.78%) obtained at 60-140% of the target analytical concentration was within limits. In addition to its high sensitivity and robustness, the intended RP-HPLC method proved reliable for stability-indicating analysis of L-carnitine even according to all analytical performance parameters. This proposed method can be used for routine quality control analysis of dosage forms and stability samples in pharmaceutical science.

Consent for publication

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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