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Statistical Assurance of Process Validation by Analytical Method Development and Validation for Celecoxib capsules

Sharma Tejal[1]*, Solanki N.S.[1], Mahatma O.P.[1], Singhai S.[2]

[1]Bhupal Noble's Girls College of Pharmacy, Udaipur (Rajasthan),India.
[2]Ranbaxy Laboratories Ltd., Dewas (M.P.),India.

Corres.author: tejalsharma123@gmail.com
Mobile: +91-9406625757

Abstract: A new simple, rapid and reliable Ultraviolet (UV) Spectrophotometry method was developed and validated for the estimation of celecoxib in blend and capsule formulations. The method was based on simple UV estimation in cost effective manner for regular laboratory analysis. The instrument used was Perkin Elmer, UV Spectrophotometer (Lambda 25) and using 0.1N HCl as solvent system. Samples were analyzed using UV Win Lab 5.2.0 software and matched quartz cells 1 cm and was monitored at 255 nm. Celecoxib was used as an internal standard. Linearity was obtained in the concentration of 2-20µg/ml for celecoxib. The validation parameters tested as per ICH guidelines prove the suitability of this method. Drug excipient interactions were not found. Statistical tools like one way analysis of variance (ANOVA) and Bonferroni's multiple comparison tests were applied on results of blend uniformity and content uniformity, done on process validation batches.
Key Words: UV Spectrophotometer, Celecoxib, Process Validation, Capsule Formulations.

Introduction

Celecoxib, 4-[5-(4- methyl phenyl) –3-(trifluoro -methyl) – 1 –H –pyrazol-1–yl]. Celecoxib is a non steroidal anti inflammatory agent (NSAID) that exhibits anti inflammatory, analgesic and antipyretic activities[1,2]. It comes under the category of Cyclooxygenase- 2 inhibitor, which acts by inhibiting prostaglandin synthesis by inhibiting COX- 2 enzyme responsible for prostaglandin synthesis. Celecoxib is given orally to treat inflammation[3].

Literature survey revealed spectrophotometric[4] and chromatographic[5,6] methods for the analysis of celecoxib. So far, no analytical methods are reported for analysis methods are reported for analysis which is looking to pharmacokinetic characteristics of drug i.e., having t_{max} of 2.9±1.2 µg/ml. The objective of this investigation is to develop, two simple, accurate and economical UV spectrophotometric[7] methods for the estimation[8] of celecoxib using 0.1 N HCl in which drug has good solubility. Dissolution

is also performed in 0.1 N HCl, looking at its Pharmacokinetic[9] and immediate release dosage form and so desired method is appropriate for analysis.

Process validation samples (blend and capsules) are withdrawn at all stages and for all three validation batches for which analysis was performed using developed method.

Experimental

Instrument

For method, Perkin Elmer UV-Vis spectrophotometer (Lambda 25, spectral bandwidth 1 nm) with 10 mm matched quartz cells; Shimadzu, Electronic Weighing Balance (AUX - 220), Oscar Ultrasonic Cleaner, Sonicator (Micro Clean 103) were used.

Procedure

Method of analysis

Standard stock solution of celecoxib was prepared by dissolving 100 mg drug in 100 ml of 0.1 N HCl (i.e., 1000 µg/ml). Aliquot of these solutions were further diluted to obtain concentration of 100 µg/ml for celecoxib and scanned in the UV range. From the spectra, wavelength 255 nm was selected as reported in Figure 1. The linearity was observed in the concentration range of 2-20 µg/ml for celecoxib. The absorptivity coefficient of drug at desired wavelengths was determined and results are presented in Table 1. The spectral data from this scan was used to determine the concentration of drug in blend and capsule sample solutions.

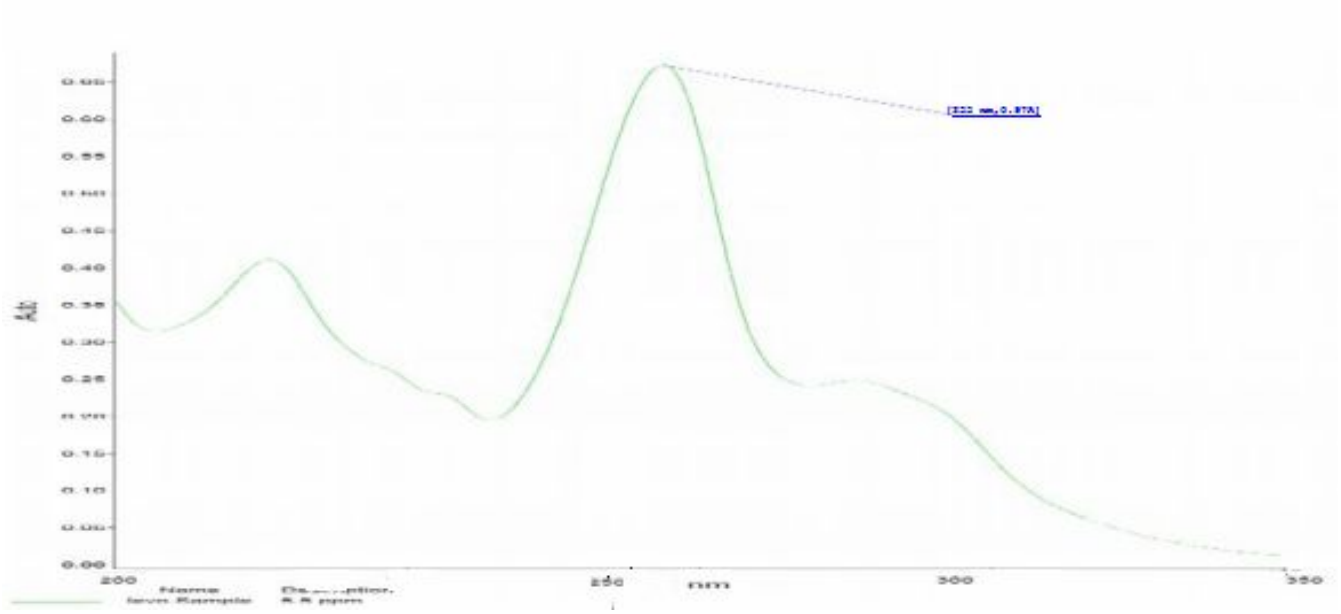

Figure 1: Spectra of Celecoxib API

Table 1: Absorptivity A(1%,1cm) values of celecoxib at 255 nm

Concentration (µg/ml)	Absorbance	A(1%,1cm) Mean ± SD	Molar absorptivity Mean ± SD
6	0.325	532.755±0.04680	20317.837±1.995

*mean of five estimations.

Analysis of Process Validation samples (Blend and capsule formulation)

Contents of twenty capsules were mixed and quantity equivalent to 60 mg of celecoxib was transferred to a series of 100 ml volumetric flasks (5 in each case), extracted with 0.1 N HCl by shaking mechanically (for Content Uniformity). Similarly blend equivalent to 60 mg celecoxib was transferred to a 100 ml calibrated volumetric flask, extracted with 0.1 N HCl by shaking mechanically (for Blend Uniformity). The solution was diluted to mark with same solvent through Whatman filter paper (no. 41). Aliquot portion of this solution was diluted to get concentration of 6 µg/ml of celecoxib. Absorbance of the sample solutions were recorded at 255 nm. The concentration of drug in samples were determined by using calibration curve. The concentration of each drug sample was determined by analysis of spectral data of sample solutions with reference standards. The results are reported in Table 2.

Recovery Studies

The recovery studies were carried out at three different levels i.e., 80%, 100% and 120%. It was performed by adding known amount of standard drug solutions of celecoxib to pre-analyzed capsule content solutions. The resulting solutions were then reanalyzed by proposed methods. The results of recovery studies are shown in Table 3 and Table 4.

Table 2: Result of assay

Label claim (mg/cap)	% Label claim*	SD	% RSD
200 mg	101.53	0.81	0.40

*mean of three estimations.

Table 3: Analysis of celecoxib API

Amount taken	Amount found*	Amount found (%)±SD	% RSD
6 µg/ml	6.09 µg/ml	101.5 ± 0.685	0.89

*mean of five estimations.

Table 4: Results of recovery studies

S. No.	Amount of drug added	% Recovery*±SD	% RSD
1.	3.2	99.6±0.41	0.43
2.	4.0	99.1±0.60	0.64
3.	4.8	98.8±0.88	0.89

*mean of three estimations at each level.

Table 5: Results of other analytical parameters

Analytical parameters	Results	%RSD
1. Precision		
a) Intra-day	100.50-100.96	0.40-1.46
b) Inter-day	100.08-100.59	0.72-1.39
c) Repeatability(n=6)	101.53±0.81	0.89
2. Specificity	A 10 µg/ml solution in 0.1 N HCl with 1%w/v sodium lauryl sulfate at 255 nm will show an absorbance of 0.540±0.0091.	
3. Linearity range	2-20 µg/ml	-
4. Ruggedness*(n=5)*		
Analyst I	99.14	0.65
Analyst II	98.96	0.74

Table 6: Blend Uniformity* (% Assay for each sample)

Batch No.	Batch 1	Batch 2	Batch 3
Mean	99.9	97.8	97.9
Minimum	99.3	94.8	95.9
Maximum	100.4	99.8	99.0
% RSD	0.4	1.3	1.0

*Final blend analyzed for 10 locations from rapid mixing granulator.

Table 7: Content Uniformity* (% Assay for each sample)

S.No.	Batch 1 Stage			Batch 2 Stage			Batch 3 Stage		
	1	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Mean	99.8	100.2	100.1	99.1	100.2	101.3	102.7	103.1	103.2
Minimum	98.9	99.6	99.6	99.5	99.3	99.3	102.1	102.6	102.7
Maximum	100.7	100.6	100.6	100.8	102	102.4	103.8	104.1	103.9
% RSD	0.53	0.36	0.32	1.08	1.09	0.68	0.71	0.52	0.43

* Ten units individual assay was analyzed for each stage of all the batches.

Results and Discussions

The proposed methods are simple, sensitive, accurate, precise, reproducible, economic and rapid for simultaneous analysis of celecoxib in capsules. Accuracy of the method was evaluated by carrying out the recovery studies. Low values of % RSD are indicative of high precision of these methods. The repeatability and ruggedness study signifies the reproducibility of the method as shown in Table 5.

Based on the validation study data, it can be concluded that the proposed method is accurate and precise for the analysis of drug. No interference was found from excipients used in capsule formulation and hence the method is suitable for analysis of blend and capsule formulations.

Process validation samples, blend uniformity was found to be good within and between all three validation batches as shown in Table 6. Filling of capsules, sample for content uniformity were collected at three stages (initial, mid, end) for all three validation batches, results for which show that there is uniformity in dosage units within batch and similarity between batches as shown in Table 7.

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