

Research Article

Titrimetric and Spectrophotometric Assay of Ganciclovir in Pharmaceuticals Using Cerium(IV) Sulphate as the Oxidimetric Agent

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Titrimetric and spectrophotometric assay of ganciclovir (GNC) is described using cerium(IV) sulphate as the oxidimetric reagent. The methods are based on the oxidation of GNC with a measured excess of cerium(IV) sulphate in acid medium followed by determination of the unreacted oxidant by two different reaction schemes. In titrimetry, the unreacted oxidant was determined by back titration with ferrous ammonium sulphate (FAS) in sulphuric acid medium, and spectrophotometry involves the reaction of residual cerium(IV) with p-DMAB to form brownish-coloured p-dimethylamino quinoneimine whose absorbance was measured at 460 nm. In both methods, the amount of cerium(IV) sulphate reacted corresponds to GNC concentration. Titrimetry is applicable over 3–10 mg range where as, in spectrophotometry, the calibration graph is linear over the range of 2–10 $\mu\text{g mL}^{-1}$ and the calculated molar absorptivity value is $1.960 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$. The validity of the proposed methods was tested by analyzing pure and dosage forms containing GNC. Statistical treatment of the results reflects that the proposed procedures are precise, accurate, and easily applicable for the determination of GNC pure form and in pharmaceutical formulations.

1. Introduction

Ganciclovir (GNC) chemically known as 2-amino-9-[[[1,3-dihydroxypropan-2-yl]oxy]methyl]-6,9-dihydro-3H-purin-6-one (Figure 1) is a nucleoside analogue widely used in the treatment of cytomegalovirus infections.

It has been proved effective against cytomegalovirus in immunocompromised patients, mainly in those with the acquired immunodeficiency syndrome (AIDS), congenital immunodeficiency, or in individuals following organ transplantation [1, 2]. Various techniques have been developed for the determination of GNC in pharmaceuticals. It is official in the United States Pharmacopoeia [3].

The most extensively used technique for the quantitation of ganciclovir is HPLC, but most of the procedures using this technique are devoted to body fluids like plasma [8–18], tissues [19], serum [20], and blood samples [21]. HPLC has also been applied for the determination of GNC in

eye drops [22]. GNC in bulk drug and in its formulations has been assayed by UV-spectrometry by measuring the absorbance of drug in 0.1 M HCl and 0.1 M NaOH at 253 and 266 nm, respectively. The methods are reported to be moderately sensitive with molar absorptivity values of $\sim 2.0 \times 10^3$. There are only three reports on the use of visible spectrophotometry for the assay of GNC in pharmaceuticals. Schelling et al. [4] have devised an enzyme kinetic method which involves the use of multiple reagents and scrupulously controlled experimental variables. The procedure also requires expensive radiolabelled substrates. Recently, Gouda [5] has reported the application of five σ - and π -acceptors for the spectrophotometric determination of GNC in its formulations *via* charge-transfer complexation reaction. The methods have been found applicable over 5–225 $\mu\text{g mL}^{-1}$ ranges with limits detection (LOD) values in the range of 0.36–2.45 $\mu\text{g mL}^{-1}$. In a very recent report, [6] Sarsambi et al. have described two procedures based on Schiff

TABLE 1: Comparison of the performance characteristics of the proposed methods with the published methods.

Sl. No.	Reagent/s used	Methodology	λ_{\max} (nm)	Linear range	LOQ ($\mu\text{g mL}^{-1}$)	Remarks	Ref.
(1)	ATP, NADH, NAD	Enzymatic	340	—	—	Requires vigorous control of experimental variables and expensive radiolabelled substrates, multiple reagents required.	[4]
(2)	σ - and π -donors	C-T complexation reaction	—	5–225 $\mu\text{g mL}^{-1}$	0.36–2.45 $\mu\text{g mL}^{-1}$	Less sensitive and multiple reagents used.	[5]
(3)	(a) p-dimethylamino-cinnamaldehyde and MBTH (b) Iron(III)-MBTH	Schiff base formation Oxidative coupling reaction	—	10–50 $\mu\text{g mL}^{-1}$ 50–250 $\mu\text{g mL}^{-1}$	—	Poorly sensitive and expensive reagents used.	[6]
(4)	Ce(IV)-rhodamine in H_2SO_4 medium	Chemiluminescence reaction	—	$5 \times 10^{-8} \text{ g mL}^{-1}$	$2.35 \times 10^{-8} \text{ g mL}^{-1}$	Requires complicated and expensive flow-injection assembly.	[7]
(5)	Ce(IV)-PDMAB IN 4 M HClO_4	Oxidative coupling reaction	460	2–10 $\mu\text{g mL}^{-1}$	0.15 $\mu\text{g mL}^{-1}$	Sensitive, inexpensive instrumental setup, use of ecofriendly chemicals, use of aqueous system.	This work

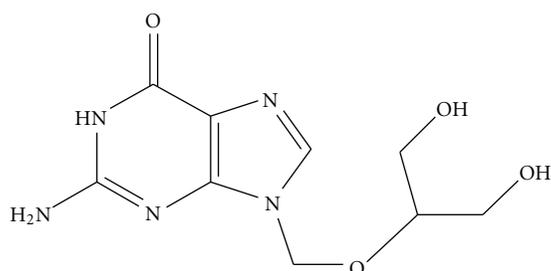


FIGURE 1: Structure of Ganciclovir.

base formation using p-dimethylamino cinnamaldehyde and oxidative coupling reaction involving the use of iron(III) and MBTH, but the methods are poorly sensitive and require heating at 40°C , with linear dynamic range of 10–50 $\mu\text{g mL}^{-1}$ and 50–250 $\mu\text{g mL}^{-1}$, respectively. The methods also employ expensive reagents. A flow injection chemiluminescence method has also been described by Wang et al. [7]. Though the method appears to be sensitive with an LOD of 2.35 $\mu\text{g mL}^{-1}$, it requires a complicated and expensive flow-injection assembly as shown in Table 1.

No titrimetric method has ever been reported for GNC despite its simplicity and versatility. In this paper, titrimetric and spectrophotometric determination of GNC is described. The methods are based on the oxidation of drug with a measured excess of Ce(IV) sulphate followed by the determination of residual oxidant either by titration with iron(II) in titrimetry or by spectrophotometry involving the use of Ce(IV) and p-DMAB. The developed methods were optimized and validated as per the guidelines of the International Conference on Harmonization [23]. The methods are important alternatives to other analytical methods with clear

advantages in terms of simplicity, cost effectiveness, speed, and sensitivity.

2. Materials and Methods

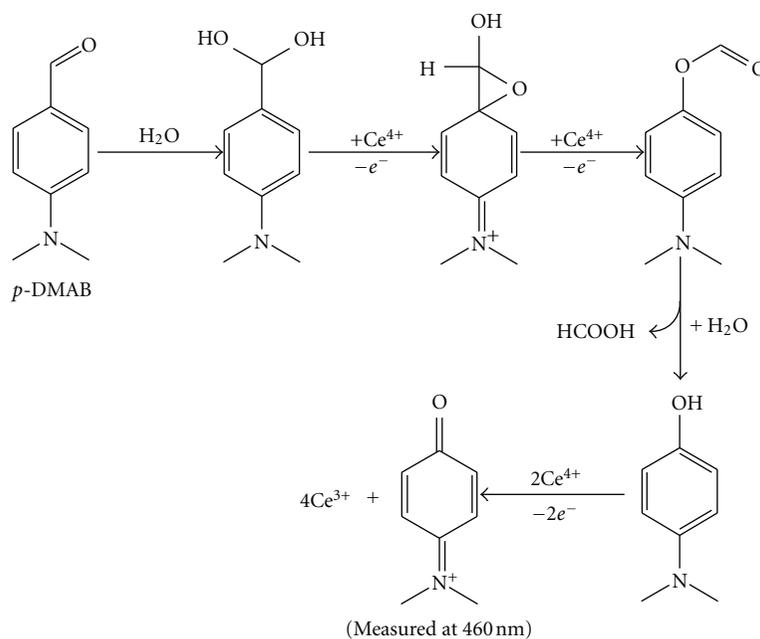
2.1. Instrument. Absorbance measurements were made on a Systronics model 106 digital spectrophotometer (Ahmedabad, India) provided with 1 cm matched quartz cells.

2.2. Material and Reagents. All chemicals and reagents used were of analytical or pharmaceutical grade and distilled water was used to prepare the solutions.

Sulphuric Acid (0.1 M; 0.5 M; 2 M; 5 M). It was prepared by appropriate dilution of the conc. H_2SO_4 (SD Fine Chem, Mumbai, India, sp. gr. 1.84) with water.

Perchloric Acid (HClO_4 ; 4 M). It was prepared by diluting concentrated acid (Merck, Mumbai, India, assay 70%) appropriately with water to get 4 M for spectrophotometric method.

Cerium(IV) Sulphate Solution (0.02 M and 300 $\mu\text{g mL}^{-1}$). A stock standard solution equivalent to 0.02 M cerium(IV) sulphate was prepared by dissolving 4.04 g of the chemical (Loba Chemie, Mumbai, India, assay 99.9%) in 14 mL of conc. H_2SO_4 and diluting to 500 mL with water in a 500 mL standard flask, mixed well, filtered using glass wool, standardized [24] and used in titrimetric work. The stock solution was then diluted appropriately with 4 M HClO_4 to obtain a working concentration of 300 $\mu\text{g mL}^{-1}$ in cerium(IV) sulphate for spectrophotometric method.



SCHEME 1: The possible reaction mechanism for the oxidation of p-DMAB by Ce(IV) in the presence of HClO₄ medium.

Ferrous Ammonium Sulphate Solution (0.02 M). A stock solution of FAS (0.02 M) was prepared by dissolving 3.92 g of the chemical (Loba Chemie, Mumbai, India, assay 99–101%) in water containing 5 mL of 0.5 M H₂SO₄ and diluted to volume in a 500 mL calibrated flask with water and used in titrimetric assay.

Ferriin Indicator Solution. It was prepared by dissolving 1.485 g of 1,10-phenanthroline monohydrate and 0.695 g of FeSO₄·7H₂O in water and diluted to 100 mL [25].

Dimethylaminobenzaldehyde (p-DMAB; 0.5%). An accurately weighed 1.25 g of p-DMAB (Merck, Mumbai, India) was transferred to a 250 mL volumetric flask, dissolved in 4 M HClO₄ and the volume was made up to the mark with the same solvent.

Standard GNC Solution (1 mg mL⁻¹ and 20 μg mL⁻¹). A stock standard solution containing 1 mg mL⁻¹ GNC was prepared by dissolving 100 mg of pure GNC in 0.1 M H₂SO₄ the volume was brought to 100 mL with water in a volumetric flask and used for titrimetric assay.

A 100 μg mL⁻¹ GNC standard solution was also prepared by dissolving an accurately weighed 10 mg of GNC in 4 M HClO₄ and diluting to the mark with the same solvent in a 100 mL calibrated flask, and this was diluted with the same solvent to get a working concentration of 20 μg mL⁻¹ GNC and used spectrophotometric method.

Two brands of tablets containing GNC, Ganguard-500 (Ranbaxy, Superspeciality Ltd., Ahamadabad, India) and Nataclovir-250 (Natco Pharma Ltd., Hyderabad, and India) used in the investigation were purchased from local commercial sources.

2.3. Methods

Titrimetry. A 10 mL aliquot of standard drug solution in 0.1 M H₂SO₄ containing 1–10 mg of GNC was measured accurately and taken in a 100 mL titration flask; 5 mL of 0.1 M H₂SO₄ and 2 mL of 2 M H₂SO₄ were added to the flask. By means of a pipette, 10 mL of 0.02 M Ce(IV)SO₄ was added, content-mixed and the flask kept aside for 15 min. Then, the unreacted cerium(IV) solution was titrated against 0.02 M FAS using ferriin indicator to a first appearance of orange red color. A blank titration was performed with 10 mL 0.1 M H₂SO₄ in place of GNC solution.

The amount of GNC in the aliquot was computed from the formula:

$$\text{Amount (mg)} = \frac{VM_w S}{n}, \quad (1)$$

where V is mL of cerium(IV) sulphate reacted, M_w is relative molecular mass of drug, S is strength of cerium(IV) sulphate, moles L⁻¹, and n is number of moles of cerium(IV) sulphate reacting with per mole of GNC.

Spectrophotometry. Varying aliquots (0.0, 1.0, 2.0, 3.0, 4.0, and 5.0 mL) of 20 μg mL⁻¹ GNC solution were transferred into a series of 10 mL calibrated flasks by means of a microburette and the total volume was adjusted to 5 mL by adding requisite volume of 4 M HClO₄. To each flask 1 mL of 300 μg mL⁻¹ Cerium(IV) sulphate was added from a microburette. The content was mixed well and the flasks were let stand for 10 min with occasional shaking. Then, was added 1 mL of 0.5% p-DMAB to each flask, again the flasks were let stand for 5 min. The volume was diluted to the mark with 4 M HClO₄, mixed well and the absorbance of each solution was measured at 460 nm against water.

TABLE 2: Sensitivity and regression parameters.

Parameter	Value
λ_{\max} , nm	460
Linear range, $\mu\text{g m}^{-1}$	2.0–10.0
Molar absorptivity (ϵ), $\text{L mol}^{-1} \text{cm}^{-1}$	1.960×10^4
Sandell sensitivity*, $\mu\text{g cm}^{-1}$	0.0132
Limit of detection (LOD), $\mu\text{g m}^{-1}$	0.05
Limit of quantification (LOQ), $\mu\text{g m}^{-1}$	0.15
Regression equation, Y^{**}	
Intercept (a)	0.7240
Slope (b)	-0.0650
Standard deviation of a (S_a)	0.4448
Standard deviation of b (S_b)	0.0703
Regression coefficient (r)	-0.9995

*Limit of determination as the weight in μg per mL of solution, which corresponds to an absorbance of $A = 0.001$ measured in a cuvette of cross-sectional area 1 cm^2 and $l = 1 \text{ cm}$. ** $Y = a + bX$, where Y is the absorbance, X is concentration in $\mu\text{g/mL}$, a is intercept, and b is slope.

A calibration graph was prepared by plotting the measured absorbance versus concentration of GNC, and the concentration of the unknown was read from the calibration graph or deduced from the regression equation derived using the Beer's law data.

Procedure for Tablets. Twenty tablets were weighed accurately and finely powdered. A quantity of the powdered tablet containing 100 mg of GNC was weighed accurately and transferred into a 100 mL calibrated flask, 60 mL of 0.1 M H_2SO_4 was added, and the content was shaken thoroughly for 15–20 min to extract the drug into the liquid phase; the volume was finally diluted to the mark with 0.1 M H_2SO_4 , mixed well and filtered using a Whatman no. 42 filter paper. First 10 mL portion of the filtrate was discarded, and a convenient aliquot of the subsequent portion of filtrate was subjected to analysis by titrimetry.

The tablet extract containing GNC at a concentration of 1 mg mL^{-1} was then diluted stepwise with 4 M HClO_4 to obtain a working concentration of $20 \mu\text{g mL}^{-1}$ in GNC and a convenient aliquot was then subjected to analysis by spectrophotometer procedure described earlier.

Placebo Blank Analysis. A placebo blank of the composition: talc (20 mg), starch (10 mg), acacia (15 mg), methyl cellulose (10 mg), sodium citrate (10 mg), magnesium stearate (15 mg), and sodium alginate (10 mg) was made and its solution was prepared as described under "procedure for tablets," and then subjected to analysis.

Procedure for the Determination of GNC in Synthetic Mixtures. To the placebo blank of the composition described above, 100 mg of pure GNC was added and homogenized, transferred to a 100 mL standard flask, and solution-prepared as described under "procedure for tablets." The resulting

solution was assayed ($n = 5$) by titrimetry according to the same procedure described above.

The synthetic mixture solution (1 mg mL^{-1} in GNC) was then diluted stepwise with 4 M HClO_4 to obtain a working concentration of $20 \mu\text{g mL}^{-1}$ in GNC for spectrophotometric method. A convenient aliquot was then subjected to analysis by spectrophotometric procedure described above. The analysis was done to study the interferences from excipients such as talc, starch, acacia, anhydrous lactose, sodium alginate, magnesium stearate, and methyl cellulose.

3. Results and Discussions

The proposed methods are indirect and are based on the determination of unreacted cerium(IV), after the reaction between GNC and the oxidant is ensured to be complete, and rely on two different well-known reactions which are shown below

GNC + Ce(IV) (known excess)



Unreacted

→ Titrated with standard FAS using ferroin indicator
(Titrimetry)

Unreacted + p-DMAB in HClO_4

→ Orange coloured product measured medium
at 460 nm (Spectrophotometry).

(2)

The titrimetric method involves oxidation of GNC by a known excess of cerium(IV) sulphate in H_2SO_4 medium and the unreacted oxidant was determined by back titration with FAS. The reaction between GNC and cerium(IV) was found to occur in 1:1 (drug:oxidant) stoichiometric ratio and all the calculations are based on this stoichiometric ratio. Using 0.02 M cerium(IV), 3–10 mg of GNC was conveniently determined.

Redox reactions always preferred highly acidic conditions. The oxidation reactions of some compounds are very rapid when perchloric acid (HClO_4) medium is maintained [26–29]. This is attributed to the highest oxidation potential of cerium(IV) in HClO_4 ($E_o = 1.75 \text{ V}$) as compared to that of cerium(IV) in H_2SO_4 ($E_o = 1.44 \text{ V}$), HNO_3 ($E_o = 1.61 \text{ V}$) or HCl ($E_o = 1.28 \text{ V}$) [30]. The greater oxidation potential of cerium(IV) in perchloric acid overcomes both the slowness of the oxidation process and the inexact stoichiometry encountered in other acids. The solutions of cerium(IV) in hydrochloric acid are unstable owing to the oxidation of chloride ions to chlorine gas [31]. The refore, in spectrophotometry, the unreacted Ce^{4+} was treated with p-DMAB in HClO_4 medium to yield formic acid and p-dimethylaminophenol, which upon further oxidation gave the corresponding quinoxaline derivative [32]. The possible reaction scheme involving the formation of coloured chromogen is given in Scheme 1.

TABLE 3: Evaluation of intraday and interday accuracy and precision.

Method*	GNC taken	Intraday accuracy and precision			Interday accuracy and precision		
		GNC found	%RE	%RSD	GNC found	%RE	%RSD
Titrimetry	3.0	3.03	1.00	1.27	2.96	1.26	2.34
	6.0	6.04	0.67	0.81	1.08	1.08	1.47
	9.0	9.02	0.22	0.66	8.94	0.66	1.62
Spectrophotometry	2.0	2.04	2.00	3.10	2.05	2.5	3.26
	4.0	4.04	1.00	1.13	4.08	2.0	1.56
	6.0	5.83	2.83	0.50	5.90	1.67	2.13

RE: relative error; RSD: relative standard deviation.

*In titrimetry, GNCs taken/found are in mg and they are $\mu\text{g mL}^{-1}$ in spectrophotometry.

TABLE 4: Method robustness and ruggedness expressed as intermediate precision (%RSD).

(a) Titrimetry

GNC taken, $\mu\text{g m}^{-1}$	Robustness		Ruggedness	
	Parameter altered		Interanalysts, (%RSD) ($n = 4$)	Interburettes, (%RSD) ($n = 4$)
	Volume of H_2SO_4^* (%RSD) ($n = 3$)	Reaction time* (%RSD) ($n = 3$)		
3.0	1.56	2.02	1.10	1.32
6.0	1.32	1.42	1.59	1.53
9.0	1.65	1.11	2.50	1.25

(b) Spectrophotometry

GNC taken, $\mu\text{g m}^{-1}$	Robustness		Ruggedness	
	Parameter altered		Interanalysts, (%RSD) ($n = 4$)	Intercuvettes, (%RSD) ($n = 4$)
	Volume of p-DMAB* (%RSD) ($n = 3$)	Reaction time* (%RSD) ($n = 3$)		
2.0	1.56	2.08	1.15	1.32
4.0	1.32	1.40	1.29	1.53
6.0	1.65	1.12	2.10	1.25

* Volumes of 5 M H_2SO_4 varied were 5 ± 1 mL, and reaction times were 15 ± 1 min.

* Volumes of p-DMAB varied were 1 ± 0.1 mL, and reaction times were 15 ± 1 min.

Optimization of Experimental Variables. The experimental variables which provided accurate and precise results were optimized.

Titrimetry. The reaction was found to be quantitative and stoichiometric in H_2SO_4 medium. A constant reaction stoichiometry of 1:1 [GNC: cerium(IV)] was obtained when 1.0–5.0 mL of 2 M H_2SO_4 was used in a total volume of 25 mL. Hence 2 mL of 2 M H_2SO_4 was used as optimum for the reaction between GNC and cerium(IV) giving an overall acidity of 0.1 M with respect to H_2SO_4 , and for the latter's back titration with iron(II). The reaction time was studied by titrating the unreacted cerium(IV) with iron(II) at different time intervals after addition of oxidant to the acidic solution of GNC. It was found that the reaction yielded a constant stoichiometry in the time range 5 to 15 min, and at the standing time less than 5 min and greater than 15 min, there was no constant and definite reaction stoichiometry. Hence, it is necessary to terminate the reaction at the end of

the fifth min by back-titrating the residual cerium(IV) with iron(II).

Spectrophotometry. Perchloric acid (4 M) medium was found necessary for rapid and quantitative reaction between GNC and Cerium(IV) and to obtain maximum and constant absorbance values due to cerium(IV)-p-DMAB reaction product at 460 nm. Therefore, all the solutions (GNC, cerium(IV) and p-DMAB) were prepared in 4 M HClO_4 throughout the investigation and the same was maintained as reaction medium. To fix the optimum concentration of Ce^{4+} , different concentrations of oxidant were reacted with a fixed concentration of p-DMAB in HClO_4 medium and the absorbance measured at 460 nm. A constant and maximum absorbance resulted with $30 \mu\text{g mL}^{-1}$ cerium(IV) sulphate and, hence, different concentrations of GNC were reacted with 1 mL of $300 \mu\text{g mL}^{-1}$ cerium(IV) sulphate in HClO_4 medium before determining the residual Ce^{4+} via the reaction scheme illustrated earlier. This facilitated

TABLE 5: Results of analysis of tablets by the proposed methods.

Tablet brand name	Label claim, mg/tablet	Found* (percent of label claim \pm SD)		
		Reference method	Titrimetry	Spectrophotometry
Ganguard 500	500	100.5 \pm 0.73%	99.2 \pm 0.63	99.9 \pm 0.53
			$t = 3.03$	$t = 0.90$
			$F = 1.33$	$F = 1.89$
Nataclovir 250	250	102.3 \pm 1.40%	100.5 \pm 1.10	100.5 \pm 1.05
			$t = 2.26$	$t = 2.30$
			$F = 1.62$	$F = 1.78$

* Mean value of five determinations.

The value of t (tabulated) at 95% confidence level and for four degrees of freedom is 2.77.

The value of F (tabulated) at 95% confidence level and for four degrees of freedom is 6.39.

TABLE 6: Accuracy assessment by recovery experiments.

Method	Tablet studied	GNC tablet*	Pure GNC added*	Total found*	Pure GNC recovered**, Percent \pm SD
Titrimetry	Ganguard 500	3.99	2.0	6.07	102.2 + 0.85
		3.99	4.0	8.19	105.0 + 0.12
		3.99	6.0	10.08	102.5 + 0.21
	Nataclovir 250	4.10	2.0	6.10	100.1 + 0.34
		4.10	4.0	8.14	101.2 + 0.11
		4.10	6.0	10.25	103.9 + 0.22
Spectrophotometry	Ganguard 500	4.13	2.0	6.18	101.4 + 0.12
		4.13	4.0	8.34	105.2 + 0.90
		4.13	6.0	10.25	103.8 + 0.56
	Nataclovir 250	3.98	2.0	6.26	107.1 + 0.12
		3.98	4.0	8.20	105.7 + 0.80
		3.98	6.0	10.17	104.8 + 0.76

* Mg in titrimetry and $\mu\text{g mL}^{-1}$ in spectrophotometry.

** Mean value of three measurements.

the optimization of the linear dynamic range over which procedure could be applied for the assay of GNC. The reaction between GNC and Ce^{4+} was complete within 15 min at room temperature ($28 \pm 2^\circ\text{C}$). After the addition of p-DMAB, a standing time of 5 min was necessary for the formation of coloured product, and thereafter, the coloured product was stable for more than an hour.

3.1. Method Validation. The proposed methods were validated for linearity, sensitivity, precision, accuracy, selectivity, and recovery.

Linearity and Sensitivity. Over the range investigated (3–10 mg GNC), a fixed stoichiometry of 1:1 (GNC: Cerium (IV) sulphate) was obtained in titrimetry which served as the basis for calculations. In spectrophotometry, under optimum conditions a linear relation was found between absorbance and concentration in the ranges given in Table 2 and Beer's law is obeyed in the inverse manner. Sensitivity parameters such as molar absorptivity and Sandel sensitivity, and limits of detection and quantification calculated as per the current ICH guidelines [23] are compiled in Table 2.

Precision and Accuracy. Intraday precision and accuracy of the proposed methods were evaluated by replicate analysis ($n = 5$) of calibration standards at three different concentration levels on the same day. Interday precision and accuracy were determined by assaying the calibration standards at the same concentration levels on five consecutive days. Precision and accuracy were based on the calculated relative standard deviation (RSD, %) and relative error (RE, %) of the found concentration compared to the theoretical one, respectively (Table 3).

Selectivity. The proposed methods were tested for selectivity by placebo blank and synthetic mixture analyses. A convenient aliquot of placebo blank solution prepared as described earlier was subjected to analysis by titrimetry and spectrophotometry according to the recommended procedures. In both the cases, there was no interference by the inactive ingredients.

A separate experiment was performed with the synthetic mixture. The analysis of synthetic mixture solution prepared above yielded percent recoveries in the range 102.7–105.4% with standard deviation of 1.31–3.15. The results of this study indicated that the inactive ingredients did not interfere

in the assay. These results further demonstrate the accuracy as well as the precision of the proposed methods.

Robustness and Ruggedness. To evaluate the robustness of the methods, reaction time and H_2SO_4 concentrations were slightly altered with reference to optimum values in titrimetry. However, in spectrophotometry, the reaction time and volume of p-DMAB were altered. To check the ruggedness, analysis was performed by four different analysts, and on three different burettes (titrimetry) or cuvettes by the same analyst. The robustness and the ruggedness were checked at three different drug levels. The intermediate precision, expressed as RSD (%), which is a measurement of robustness and ruggedness, was within the acceptable limits (0.72–3.74%) as shown in Table 4.

Applicability of the Proposed Methods. The proposed methods were successfully applied to the determination of GNC in pharmaceutical preparations. The results obtained by the proposed methods were compared to those of the reference method [5] by applying Student's *t*-test for accuracy and *F*-test for precision. The results (Table 5) show that the Student's *t*- and *F* values at 95% confidence level are less than the theoretical values, which confirmed that there is no significant difference in the performance of the proposed methods and the reference method with respect to accuracy and precision.

Recovery Studies. The accuracy and validity of the proposed methods were further ascertained by performing recovery studies. Preanalysed tablet powder was spiked with pure GNC at three concentration levels (50, 100, and 150% of that in tablet powder) and the total was found by the proposed methods. In all cases, the added GNC recovery percentage values ranged between 101.7 and 109.7% with standard deviation of 0.54–2.42 (Table 6) indicating that the recovery was good and that the coformulated substance did not interfere in the determination.

4. Conclusions

The proposed titrimetric and spectrophotometric methods using Ce(IV)SO_4 have suitable performance characteristics for application in the determination of ganciclovir. In particular, the titrimetry is much simpler in technique, more rapid than all the methods reported so far for ganciclovir. The proposed spectrophotometric method employs mild working conditions without heating or extraction and as sensitive as many reported methods. The methods are also useful due to high tolerance limit for common excipients found in drug formulations. Hence, these advantages encourage the application of the proposed methods in routine quality control analysis of ganciclovir in pharmaceutical industries.

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