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Research Article

STABILITY INDICATING RPHPLC METHOD FOR THE DEVELOPMENT AND VALIDATION OF CARBOPROST IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT
Pharmaceutic dose form and bulk form: Carboprost via RP-HPLC Methodology Carboprost's absorption maxima turned out to be 228.0 nm. Agilent C18 150 mm 4.6 mm 5 µm X 100 Å stationary phase Agilent conditions; mobile phase 1N Citrate buffer; methylene chloride and water in a 55:45 ratio. Next pH changed to 3.5. Furthermore, flow rate was kept at 1.1 ml/min; the detection wave length was 228 nm; column temperature was set at 26.0oC; and diluent was mobile phase. Conditions were determined as ideal approach. Carboprost's retention period turned shown to be 2.295 min. The Carboprost's % RSD turned out to be 0.4% correspondingly. %Recovery came up as 99.90% for Carboprost correspondingly. Carboprost's LOD, LOQ values from its regression equations came out as 0.04 and 0.11 respectively. For Carboprost especially, %Assay came out as 99.80%. Carboprost's equation of regression is y = 52769x + 663.92. Retention periods were lowered and run durations were lowered; so, the created approach was easy and cost-effective that one could apply in routine Quality control tests in different industries. Carboprost degradation investigations were conducted with an acceptable range and a greater than purity angle threshold in all conditions.

Key Words: Carboprost, Method development, Validation, RP-HPLC.

INTRODUCTION[1-10]
Carboprost tromethamine is a synthetic analog of prostaglandin F2α, widely used in obstetric and gynecologic practice for its potent uterotonic properties. It is primarily administered to manage postpartum hemorrhage (PPH) due to uterine atony, which is one of the leading causes of maternal morbidity and mortality globally. By promoting strong uterine contractions, carboprost effectively reduces blood loss in the postpartum period when first-line interventions like oxytocin are insufficient. Carboprost is also utilized for second-trimester pregnancy termination in cases of intrauterine fetal death or when legally indicated.

Carboprost exerts its effects through binding to prostaglandin F2α receptors on the smooth muscle cells of the uterus, inducing strong, rhythmic contractions. This increased uterine tone helps constrict blood vessels, thereby reducing uterine bleeding. The drug is typically administered via intramuscular injection, and its effects are often rapid, making it suitable for emergency situations such as severe postpartum hemorrhage.

The efficacy of carboprost in controlling PPH has been well-documented, particularly in cases where oxytocin and other uterotonic agents fail to achieve adequate control. However, its use is associated with certain side effects, most notably gastrointestinal disturbances (such as nausea, vomiting, and diarrhea), as well as fever, bronchospasm, and hypertension. As a result, carboprost is generally reserved for cases where other uterotonic agents have proven ineffective, or when rapid control of bleeding is necessary to stabilize the patient.

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In clinical practice, carboprost has become an essential tool in the management of obstetric emergencies. Its ability to quickly induce strong uterine contractions makes it highly effective in preventing maternal mortality associated with postpartum hemorrhage. However, its side effects and contraindications, such as in patients with asthma or significant cardiovascular disease, require careful consideration when administering the drug.

Carboprost remains a crucial therapeutic option in obstetrics, particularly in the management of postpartum hemorrhage and induced abortion. Its ability to rapidly induce uterine contractions makes it indispensable in situations where bleeding must be controlled quickly. While side effects can be significant, careful patient selection and monitoring help mitigate these risks, making carboprost a valuable drug in modern obstetric care.

Analytical Background[11]

Carboprost is a synthetic prostaglandin. It binds the prostaglandin E2 receptor, causing myometrial contractions, casuing the induction of labour or the expulsion of the placenta. Prostaglandins occur naturally in the body and act at several sites in the body including the womb (uterus). They act on the muscles of the womb, causing them to contract. It is chemically known as (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-3-methyloct-1-en-1-yl]cyclopentyl]hept-5-enoic acid; 2-amino-2-(hydroxymethyl)propane-1,3-diol.

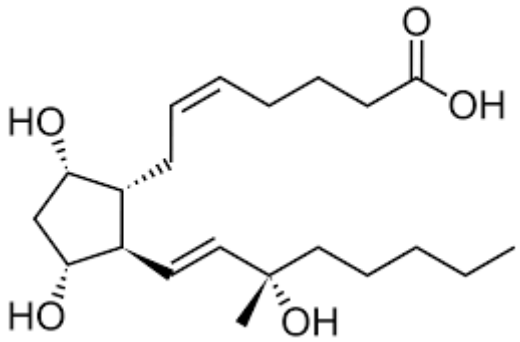

Figure 1 Structure of Carboprost

High Performance Liquid Chromatography (HPLC) plays a crucial role in the validation of Carboprost, In the review of literature, more economical methods were observed [12-16], hence a simple, cost-effective stability-indicating simultaneous estimation of Carboprost by RP-HPLC in pharmaceutical dosage form must be developed and validated as per the guidelines of ICH (Q2 specification).

MATERIALS:

Carboprost pure drug (API), Carboprost formulation (Carboprost - 250), Distilled water, Acetonitrile, Phosphate buffer, Methanol, Potassium dihydrogen ortho phosphate buffer, Ortho-phosphoric acid. All the above chemicals and solvents are from Rankem.

INSTRUMENTATION

The development and method validation were conducted using a WATERS HPLC, specifically the model 2695 SYSTEM, equipped with a Photo diode array detector. The system also included an automated sample injector and the Empower 2 software.

Table 1: Chromatographic Conditions:

Mobile phase	1N Citrate buffer : dichloromethane and water(55:45 v/v)
Flow rate	1.1 ml/min
Column	Agilent C18 (4.6 x 150mm, 5µm)
wave length	228 nm
Column temperature	30°C
Injection volume	10µL
Run time	10.0 min
Buffer	1N Citrate buffer

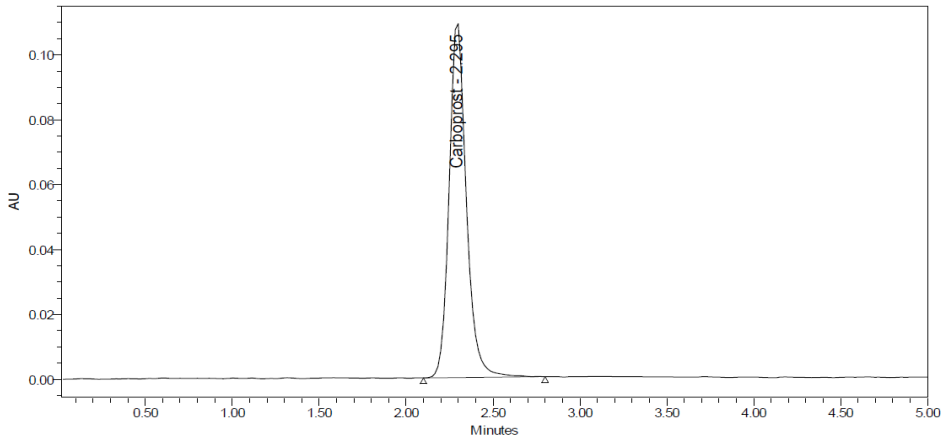

Figure 2: Optimized Chromatogram

Methods:

Preparation of Standard stock solutions: Accurately weighed 12.5mg of Carboprost transferred to 100 mL volumetric flask separately. 50ml of Diluent was added to flask and sonicated for 20mins. Flasks were made up with Water: Methanol (70:30 v/v) and labeled as Standard stock solution 1. (125ppm of Carboprost)

Preparation of Standard working solutions (100% solution): 1ml from stock solution was pipette out, taken into a 10ml volumetric flask, and made up with Water: Methanol (70:30 v/v) (12.5ppm of Carboprost)

Preparation of Sample stock solutions: 1 vial of injection (equivalent to 250mcg dosage form) wea taken and transferred into a 10 mL volumetric flask, 5mL of diluent added and sonicated for 20 min, further the volume made up with diluent and filtered with o.45 um nylon filter. (25ppm of Carboprost)

Preparation of Sample working solutions (100% solution): From the filtered solution 5ml was pipette out into a 10 ml volumetric flask and made up to 10ml with diluents. (12.5ppm of Carboprost)

Validation:

System suitability parameters:

The system suitability parameters were determined by preparing standard solution of Carboprost (12.5 ppm) and the solution were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should not be more than 2%.

Specificity (Selectivity): Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So, this method was said to be specific. Representative chromatogram is shown in Figure 3 and experimental data is given in Table 2

Table: 2 System suitability parameters for Carboprost

S no	Carboprost		
Inj	RT(min)	USP Plate Count	Tailing
1	2.283	3038	1.18
2	2.293	2962	1.17
3	2.295	3010	1.19
4	2.297	2967	1.16
5	2.300	3081	1.18
6	2.302	3032	1.18

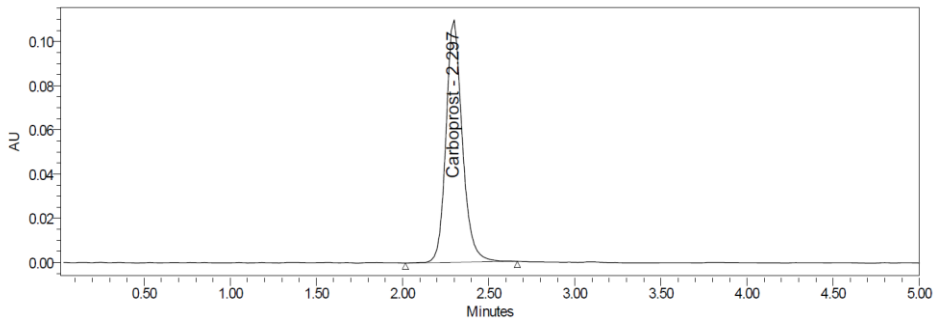

Figure 3: System Suitability Chromatogram of Carboprost

Table 3: Specificity Data

Peak name	Rt	Area	USP plate count	Tailing
Carboprost	2.295	664779	224.9	1.2

Specificity:

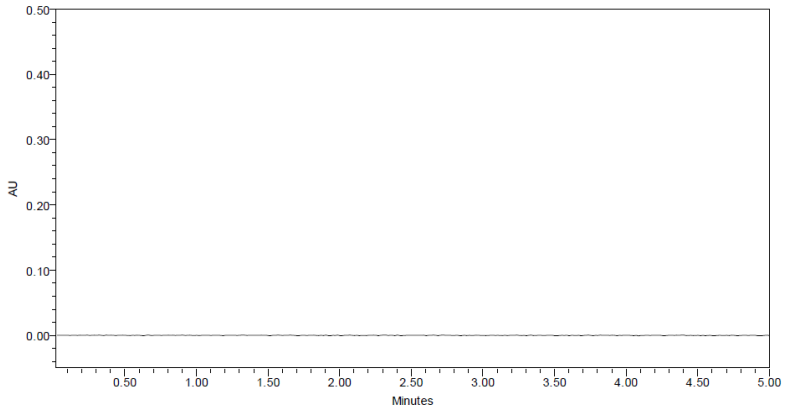

Figure 4 Chromatogram of blank.

The forced degradation conditions are mentioned in Table 4 and the results are mentioned in Table 5

Table 4: Forced degradation conditions for Carboprost

Stress condition	Solvent	Temp(^{0}C)	Exposed time
Acid	2N HCL	60^{0}c	30 mins
Base	2N NAOH	60^{0}c	30 mins
Oxdation	20% H_2O_2	60^{0}c	30 mins
Thermal	Diluent	105^{0}c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^{0}c	

From the results, degradation peaks were observed when the samples were exposed to acid. According to the stress study, none of the degradant co-eluted with the active drug peaks formed.

Table 5: Degradation profile results

Degradation Condition	% Drug Degraded	% Drug UnDegraded
Acid	1.74	98.26
Base	6.06	93.94
Oxidation	5.73	94.27
Thermal	1.72	98.28
Photolytic	0.21	99.79
Hydrolytic	1.23	98.77

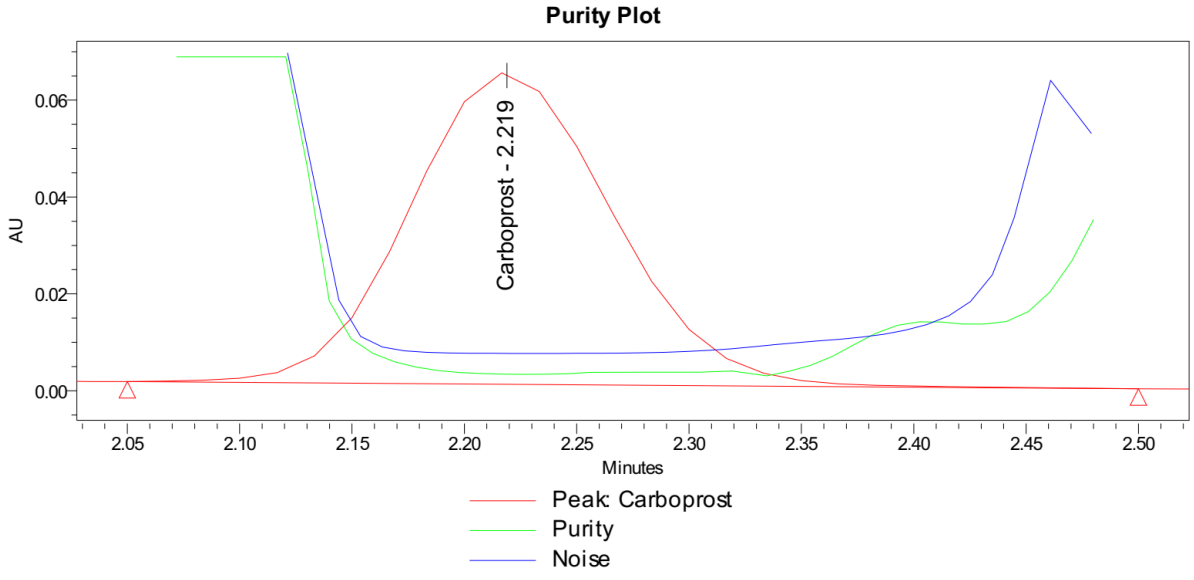

Figure 5: Purity Plot of Acid

Limit of detection (LOD) The detection limit is considered as very low level of concentration of an analyte in a sample that can be detected, but not necessarily quantitated.
Limit of quantitation (LOQ): The limit of quantitation is considered as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy of the method.
The LOD values obtained for Carboprost are listed in Table 6.

Table 6: Summary of limit of detection

Sample	Conc (µg/ml)
LOD	0.04
LOQ	0.11

Linearity: The linearity of the method was demonstrated for Carboprost by analyzing the solutions ranging from 25% to 150% of the specification limit (Table 7). The correlation coefficient for Carboprost was 0.999. This indicates good linearity

Linearity:
Calibration data is given in table 7 and regression data in table 8 and calibration curve in figure 6

Table 7: Calibration data of Carboprost

Carboprost	
Conc (µg/mL)	**Peak area**
0	0
3.12	167043
6.25	330354
9.38	492168
12.5	665942
15.6	814736
18.75	995368

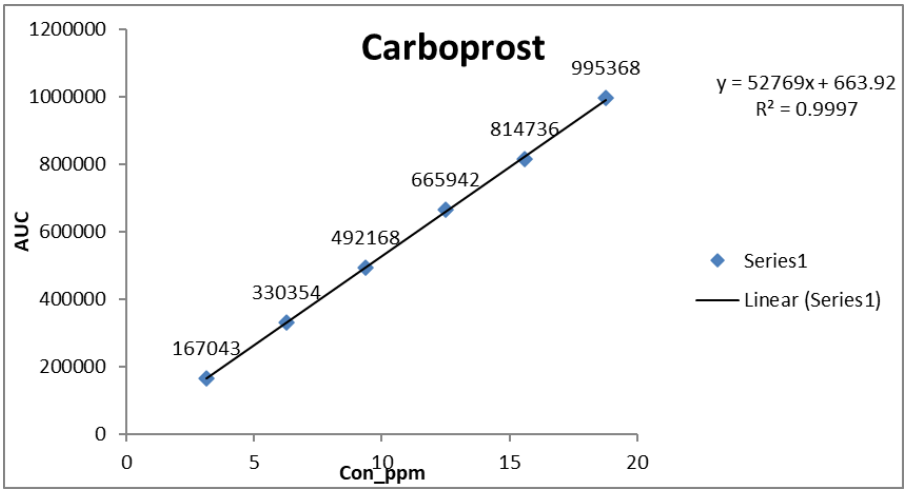

Figure 6: Calibration curve of Carboprost

Table 8: regression data

Parameter	Carboprost
Conc range (µg/mL)	3.12-18.75µg/ml
Regression Equation	y = 52769x + 663.92
Co-relation	0.999

Accuracy: The accuracy of the method was determined by using solutions containing spiked samples of Carboprost at 50%, 100% and 150% of the working strength. All the solutions were prepared in triplicate and analysed. The percentage recovery results obtained for each impurity was listed in Table 9

Table 9 Accuracy table of Carboprost

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% recovery
50%	6.25	6.28	100.54
	6.25	6.21	99.40
	6.25	6.24	99.88
100%	12.5	12.50	100.04
	12.5	12.53	100.23
	12.5	12.53	100.22
150%	18.75	18.74	99.97
	18.75	18.65	99.47
	18.75	18.63	99.39
Mean % recovery			99.90

System Precision: The system precision was performed by analyzing six replicate injections of standard solution at 100% of the specified limit with respect to the working strength of Carboprost. Results of peak area are summarized in Table 10

Table 10 System precision table of Carboprost

S. No	Area of Carboprost
1.	665305
2.	668822
3.	668162
4.	661399
5.	664714
6.	663591
Mean	**665332**
S.D	**2795.4**
%RSD	**0.4**

Method Precision: The precision of the method was determined by analyzing a sample of Carboprost). Data obtained is summarized in Table 11

Table 11 Repeatability table of Carboprost

S. No	Area of Carboprost
1.	665305
2.	668822
3.	668162
4.	661399
5.	664714
6.	663591
Mean	**665332**
S.D	**2795.4**
%RSD	**0.4**

Intermediate precision: It is differently from the repeatability, the precision obtained within a single laboratory over a longer period (generally at least several months) and considers more changes than repeatability. Data obtained is summarized in Table 12

Table 12 Intermediate precision table of Carboprost

S. No	Area of Carboprost
1.	669676
2.	661395
3.	670435
4.	663866
5.	662862
6.	663654
Mean	**665315**
S.D	**3780.9**
%RSD	**0.6**

Robustness: The chromatographic conditions were deliberately changed to evaluate the robustness of the existing method. To determine the robustness of method, system suitability solution is prepared as per methodology and injected into HPLC at different altered conditions to check the method's ability like flow rate (± 10%), column oven temperature (± 5°C) and Mobile phase (± 10%) from actual method conditions. No significant change is observed by changing flow, temperature, Mobile phase, and system suitability also complied as per methodology. The robustness results are summarized in Table 13.

Table 13 Robustness data for Carboprost

Condition	%RSD of Carboprost
Flow rate (-) 0.9ml/min	1.0
Flow rate (+) 1.1ml/min	0.2
Mobile phase (-) 50B:50A	0.3
Mobile phase (+) 60B:40A	0.4
Temperature (-) 27°C	0.7
Temperature (+) 33°C	0.6

Assay data: -

Carboprost - 250 Tablet bearing the label claims Carboprost 300 mg. Assay was performed with the above formulation. Average % Assay for Carboprost obtained was 99.47% respectively. Assay data shown in table no 14.

Formula to calculate assay:

$$\%\ \text{Assay} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{10} \times \frac{10}{1} \times \frac{P}{5} \times \frac{FV}{100} \times \frac{}{L.C} \times 100$$

AT	Average Peak area of Carboprost in test solution
AS	Mean peak area of Carboprost in standard solution
WS	Weight of Carboprost working standard taken in mg
P	Assay of Carboprost working standard in % on dried basis
L.C	Label Claim
FV	Filled volume(1ml of a vail)

Table 14: Assay Data of Carboprost

S.no	Standard Area	Sample area	% Assay
1	665305	669676	100.45
2	668822	661395	99.21
3	668162	670435	100.57
4	661399	663866	99.58
5	664714	662862	99.43
6	663591	663654	99.55
Avg	**665332**	**665315**	**99.80**
Stdev	**2795.4**	**3780.9**	**0.57**
%RSD	**0.4**	**0.6**	**0.6**

CONCLUSION

The outcomes of the Carboprost HPLC investigation indicate that this approach can precisely measure the concentration and purity of the medication. This method is ideal for pharmacokinetic studies and routine quality control due to its capacity for repeated usage with sharp peak resolutions and consistent retention times. Ensuring Carboprost's efficacy and safety for medical use, along with verifying its chemical makeup, relies on HPLC analysis.

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