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Data-driven quality assessment of polyoxyl 40 hydrogenated castor oil: utilizing CART® modeling to define critical thresholds for chemical stability

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Abstract

Polyoxyl 40 hydrogenated castor oil (PHCO) is a widely utilized non-ionic surfactant and solubilizer in the pharmaceutical industry. Ensuring the batch-to-batch consistency of its chemical quality attributes, particularly the acid value (AV), is critical for the stability and shelf-life of finished dosage forms. This study investigates the application of classification and regression tree (CART®) modeling as a predictive tool for quality assessment in an industrial manufacturing setting. Using a dataset of 48 industrial batches sourced from an Asian manufacturing facility and analyzed in strict accordance with United States Pharmacopeia (USP) standards, seven quality predictors were evaluated: temperature of turbidity, congealing temperature, hydroxyl value, iodine value (IV), saponification value, water content (WC), and residue on ignition. The statistical analysis, conducted via Minitab with 10-fold cross-validation, produced an optimal 2-node regression tree to minimize the risk of overfitting. Results identified IV as the most significant predictor of acidity, achieving 100% relative importance, followed by WC (71.9%) and hydroxyl value (52.6%). The model revealed a definitive non-linear threshold at IV ≤ 0.45; batches meeting this criterion demonstrated a mean AV of 0.256, while those exceeding this limit showed a significantly higher mean AV of 0.968. The model attained a training R-squared of 42.68% and a test R-squared of 34.85%. These findings suggest that saturation levels and moisture content are the primary drivers of acidity, likely due to the hydrolysis of ester bonds within the polyoxyl chain. This study demonstrates that CART modeling provides robust, actionable decision rules that enhance Quality by Design (QbD) frameworks.

Keywords: Polyoxyl 40 hydrogenated castor oil; CART modeling; Acid value; Quality by design (QbD); USP standards; Predictive analytics

Introduction

Polyoxyl 40 hydrogenated castor oil; a non-ionic surfactant; is a complex mixture of the tri-esters of glycerin with 12-hydroxystearic acid; ethoxylated with approximately 40 units of ethylene oxide (represented by the variables x; y; and z) as shown in Figure 1 (Limpakomon *et al.* 2019; USP, 2024). The molecule's amphiphilic nature—combining a hydrophobic hydrogenated castor oil core with hydrophilic polyethylene glycol chains—is fundamental to its role as a solubilizer (Kishore *et al.* 2011; Mahboubifar *et al.* 2016). The chemical stability of this structure is primarily monitored through the acid value (AV); which tracks potential ester hydrolysis; and the iodine value (IV); which confirms the saturation of the fatty acid chains.

Polyoxyl 40 hydrogenated castor oil, widely known by trade names like Cremophor RH40, is a versatile, non-ionic surfactant and solubilizer used predominantly in the pharmaceutical, cosmetic, and personal care industriesto emulsify and dissolve hydrophobic substances in water-based formulations. In pharmaceuticals, it acts as a solubilizing agent for vitamins, essential oils, and poorly soluble API drugs, improving their bioavailability in oral, topical, and even injectable preparations. In cosmetics, this pale-yellow, waxy substance functions as an emulsifier, emollient, and cleansing agent, providing stability and a smooth texture to lotions, creams, shampoos, and hair styling products.

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Additionally, it acts as a foam booster in liquid cleansers, a fragrance solubilizer in perfumes and aftershaves, and can improve the transparency of various water-based products (Singh, 2018; Naseriyeh and Mirzaei, 2025; Qelliny *et al.* 2025; Special Chem, 2025; Muby Chem, 2025; Libraw Pharma, 2025). Due to its high compatibility, it is often employed to create stable emulsions and increase the solubility of hydrophobic substances in both aqueous and alcoholic solutions.

Although official pharmacopeias thoroughly define the chemical characteristics of polyoxyl 40 hydrogenated castor oil; navigating the relationships between these properties usually relies on trial-and-error methods (Limpakomon *et al.* 2019; Al-Suwayeh *et al.* 2023; USP, 2024). This research aimed to introduce several innovations: Identifying Non-Linear Thresholds: The study goes beyond basic correlations to pinpoint a critical "tipping point" for key inspection metrics; ensuring compliance with acid value standards. Predictor Hierarchy: It establishes a ranked; actionable hierarchy for process engineers; clearly distinguishing the impact of impurities from that of process settings. Digital Quality Approach: The study aligns manufacturing with a " Predictive Control Strategy" philosophy; utilizing an AI-driven model to ensure consistent; reproducible quality predictions across varying input conditions; thus reducing batch-to-batch variability.

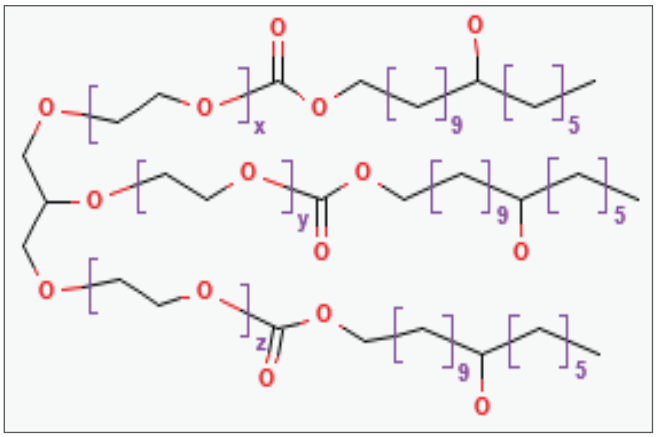

Fig. 1. Representative molecular structure of polyoxyl 40 hydrogenated castor oil. The central glycerol-derived core contains the ester linkages (C=O-O groups connecting the fatty acid chains), which are the primary sites for hydrolytic cleavage. The surrounding polyoxyl chains (denoted by subscripts x, y, and z) represent the hydrophilic ethylene oxide units. [Source: https://pubchem. ncbi.nlm.nih.gov/ substance/ 135283603]

The primary objective of this research is to establish a predictive, non-linear model for the chemical stability and purity of polyoxyl 40 hydrogenated castor oil (PHCO) using classification and regression tree (CART®) analysis. Specifically, the study aims to: Identify the Critical Quality Attributes (CQAs) and process parameters that exert the most significant influence on the acid value (AV); a primary indicator of batch stability and ester hydrolysis. Determine quantifiable decision-rule thresholds (e.g.; iodine value limits) that can be used in a manufacturing environment to predict and prevent batch failures. Evaluate the effectiveness of machine learning-based recursive partitioning as a troubleshooting tool compared to traditional linear statistical methods in pharmaceutical excipient quality control.

Materials and methods

The research focuses on the acid value as the dependent response variable due to its role in representing the chemical integrity of the ethoxylated castor oil structure. The study utilizes a x-node CART® regression model with 10-fold cross-validation to ensure the robustness of the discovered rules. The scope is limited to identifying macro-level predictors of quality to streamline industrial "release-by-exception" protocols and enhance process consistency (ICH,1994).

Data sourcing

The study utilized data from 48 industrial batches of polyoxyl 40 hydrogenated castor oil (PHCO). The samples were produced and analyzed by an Asian manufacturing company located in Asia developing country, specializing in pharmaceutical excipients (Eissa, 2024; Eissa, 2025). Each batch was manufactured using the controlled ethoxylation of hydrogenated castor oil to meet international pharmacopeial standards (USP, 2024). The dataset was organized into a flat-table format; with each row representing a unique production batch and columns representing the physical and chemical quality attributes in Excel database.

Laboratory analysis (USP Standards)

All laboratory testing was performed in an ISO-certified quality control laboratory in the firm. Samples were analyzed in strict accordance with the United States Pharmacopeia (USP) monographs for polyoxyl 40 hydrogenated castor oil and general chapter <401> Fats and Fixed Oils in the laboratory (USP, 2024). The scope of

this investigation encompasses the analysis of multi-batch production data for Polyoxyl 40 hydrogenated castor oil. The study evaluates a range of physical and chemical predictors; including the following parameters which were measured to determine compliance with USP specifications:

Acid value (AV)

Determined by titration; USP limit: NMT 2.0.

Hydroxyl value (HV)

Measured via acetic anhydride acetylation; USP range: 60–80.

Iodine value (IV)

Determined by the Wijs method to assess saturation; USP limit: NMT 2.0.

Saponification value (SV)

USP range: 45–69.

Temperature of turbidity (TempTur)

Measured as the temperature at which a 1 in 10 aqueous solution becomes turbid; USP range: 70.0°C–85.0°C.

Congealing Temperature (CongT)

Determined as per USP <651>; USP range: 16.0°C–26.0°C.

Water content (WC)

Measured via Karl Fischer titration; USP limit: NMT 3.0%.

Residue on ignition (ROI)

Determined as per USP <281>; USP limit: NMT 0.3%.

Statistical analysis and predictive modeling

Statistical modeling was conducted using Minitab® (Version 21.x or latest); specifically utilizing the Predictive Analytics Module for CART® (Minitab LLC, 2021). The objective of modeling was to predict the acid value (AV) based on the remaining seven physical and chemical predictors. The CART algorithm was configured with the following parameters to ensure a robust and consistent output; adhering to "one standard error (SE) rule" (or "one-SE rule") to identify the most parsimonious optimal tree.

Regression method

Node splitting was performed using the Least Squared Error criterion to minimize the sum of squared deviations from the mean in each node.

Validation method

To account for the sample size (n=48); 10-fold cross-validation was applied. The data was partitioned into 10 subsets (folds); with each fold serving as a test set for a model trained on the remaining 9 folds.

Tree selection

The optimal tree was identified as the smallest tree with an R-squared value within 1 standard error of the maximum R-squared; a strategy employed to prevent overfitting.

Model performance metrics

The model's predictive accuracy was evaluated using the Training R-squared; Test R-squared; and Root Mean Squared Error (RMSE) for both datasets.

Variable importance

Predictors were ranked based on their contribution to the reduction of error during node splits; with values normalized relative to the top predictor (100%).

Results and discussion

Descriptive statistics of the response variable

The descriptive statistics for the acid value (AV) of the 48 analyzed batches of Polyoxyl 40 hydrogenated castor oil are

Table I. Descriptive statistics for acid value (AV) of polyoxyl 40 hydrogenated castor oil (n=48) (mg KOH/g)

Mean	StDev	Minimum	Q1	Median	Q3	Maximum
0.612083	0.551053	0.1	0.1	0.3	1.1	1.8

Note: All values are reported in mg KOH/g. The upper specification limit (USL) for Acid Value according to USP monographs is not more than (NMT) 2.0.

presented in Table I. The dataset reveals a mean acid value of 0.612 and a median of 0.300. The standard deviation of 0.551 indicates substantial variability within the production process relative to the mean.

Analysis of optimal tree diagram and implication

The results of the 2-node CART® regression analysis, as visualized in the optimal tree diagram, demonstrate that the iodine value (IV) serves as the singular most critical determinant for partitioning the acid value (AV) of polyoxyl 40 hydrogenated castor oil. The model initiates at a root node with a global mean AV of 0.612083 (n = 48) and utilizes a primary split threshold of ≤ 0.45 for the iodine value. This recursive partitioning effectively bifurcates the dataset into two distinct terminal nodes with significant variance in their response means. Terminal Node 1; representing batches with an IV NMT ≤ 0.45; exhibits a substantially lower mean AV of 0.255833 and a narrowed standard deviation of 0.295422. In contrast, Terminal Node 2 contains batches where the IV NMT exceeds 0.45; resulting in a significantly elevated mean AV of 0.968333 and increased internal variability (StDev = 0.503551). This indicates a clear non-linear relationship where lower levels of unsaturation—as indicated by a lower iodine value—directly correlate with enhanced chemical stability and lower acidity in the final excipient. Practically, these results suggest that maintaining the iodine value below the 0.45 threshold is a critical process control strategy for ensuring batch consistency and meeting high-purity quality specifications (Karl, 2017). This can be concluded from optimal tree diagram in Figure 2.

A higher iodine value (IV) indicates a greater concentration of carbon-carbon double bonds (unsaturation) within the fatty acid chains of the polyoxyl 40 hydrogenated castor oil. Chemically, these double bonds act as reactive sites that are highly susceptible to oxidative degradation and autoxidation. When these unsaturated chains are exposed to environmental factors during processing or storage, they can undergo oxidative cleavage, leading to the formation of hydroperoxides and the subsequent breakdown into smaller, acidic byproducts—specifically free fatty acids. Because the acid value (AV) is a direct measure of these free carboxylic acid groups, the presence of residual unsaturation (as marked by a high IV) fundamentally compromises the chemical stability of the excipient, driving the AV higher.

It is important to note that while the IV threshold of ≤ 0.45 was derived from a specific industrial dataset, it represents a significantly more stringent internal control than the current USP limit. We propose this value not as a universal regulatory standard, but as a site-specific 'gold standard' for high-stability batches. Other manufacturing facilities may utilize this CART® methodology to determine their own optimized thresholds, which may vary slightly depending on their specific ethoxylation equipment and raw material sources.

Model performance and predictive validation

The predictive integrity of the CART® model was evaluated using a comprehensive suite of error metrics; comparing the performance on the training dataset against the 10-fold cross-validation test results. These statistics are summarized in Table II. The model achieved a training R^2 of 42.68%; indicating that the selected predictors explain nearly half of the total variance in the acid value. The transition to the test dataset showed an R^2 of 34.85%; a reduction of approximately 7.83%. This relatively small gap between training and testing performance suggests that the model possesses a satisfactory degree of generalizability and is not significantly overfitted, despite the complex nature of the industrial ethoxylation process (Rachmawati *et al.* 2017; USP, 2024).

The error metrics—specifically the RMSE and MAD—remained consistent across both phases. The training RMSE of 0.4128 and the test RMSE of 0.4401 provide a quantifiable measure of the model's accuracy; suggesting that predicted acid values typically deviate from laboratory-measured values by less than 0.45 units. Furthermore, the mean absolute percent error (MAPE) remained remarkably stable at approximately 1.04% to 1.06%; underscoring the high precision of the binary partitioning logic.

From a practical significance standpoint, while an R^2 of ~35% indicates that additional latent variables (such as reaction time or catalyst concentration) may influence acidity; beyond the chemical attributes measured, the remaining variance in acid value (approximately 65%) is likely attributed to specific manufacturing process variables that were not captured in the laboratory dataset. Key factors include reaction duration and the temperature profile during the ethoxylation phase; prolonged exposure to high temperatures can accelerate thermal degradation and ester bond cleavage. Furthermore, the catalyst type (e.g., alkaline catalysts like KOH) and its residual concentration can significantly influence the rate of side reactions during synthesis. Other latent variables, such as agitation efficiency (affecting thermal homogeneity within the reactor), the purity of the ethylene oxide gas, and the cooling rate post-reaction, are also critical determinants of the final chemical stability and acidity of the excipient. The current model remains highly effective as a screening tool. By utilizing the major predictors like iodine value and water content, the model

provides a reliable early-warning system for identifying batches at risk of high acidity before they reach the final stages of quality release.

Given the observed Test R^2 of 34.85% , it is important to explicitly state that this model is intended as a quality screening tool for industrial batch categorization rather than

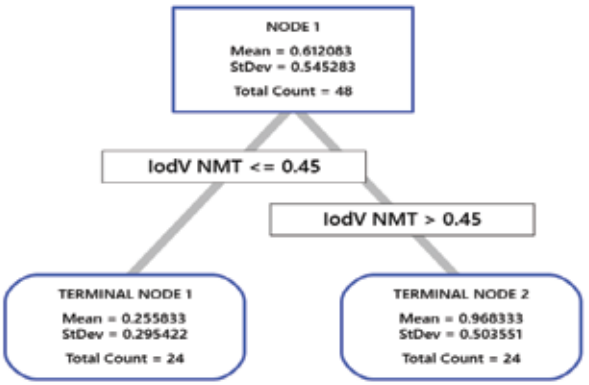

Fig. 2. Optimal Tree Diagram. The decision logic of the model shows the primary split at IV NMT ≤ 0.45 (g I_2/100g); which separates the data into two distinct clusters of acid values (mg KOH/g)

a high-precision quantitative predictor of absolute acid value units. Its primary value lies in its ability to reliably partition batches into 'low-risk' and 'high-risk' quality tiers using established thresholds.

3). Water content (WC) follows as a critical secondary predictor with a relative importance of 71.9%; indicating that moisture levels significantly influence the chemical stability and potential for ester hydrolysis in the batches. The high relative importance of water content (71.9%) confirms its role as a key reactant and kinetic driver in the degradation of PHCO. In an industrial context, residual moisture acts as the medium for the hydrolysis of ester bonds, where the rate of free fatty acid formation is directly proportional to the available water molecules. This establishes moisture control not just as a purity requirement, but as a critical kinetic barrier against the rise of acid value during storage. Other significant chemical attributes include the hydroxyl value (HydV) at 52.6% and the saponification value (SV) at 46.3%; while the temperature of turbidity (TempTur) shows a moderate impact at 37.3%. Interestingly, physical and trace markers such as residue on ignition (ROI) and congealing temperature (CongT) contributed minimally to the model; with scores of 2.9% and 2.4% respectively. These rankings suggest that the saturation level and moisture content are the dominant drivers of acidity, providing a clear hierarchy for manufacturers to prioritize analytical focus during quality control assessments.

The Scatterplot of Response Fits vs. Actual Values provides a visual assessment of the CART® model's predictive accuracy for both the training and test datasets (Figure 4). The graph displays two distinct horizontal clusters of predicted acid values, corresponding to the binary terminal nodes generated by the iodine value split. In both the training and test phases, the model successfully differentiates between low-acidity batches (predicted at ~0.25) and high-acidity batches (predicted at ~0.97); closely mirroring the distribution of the

Table II. Comparative model performance statistics for acid value prediction

Statistics *	Training	Test (Cross -Validation)
R-squared	42.68%	34.85%
Root mean squared error (RMSE)	0.4128	0.4401
Mean squared error (MSE)	0.1704	0.1937
Mean absolute deviation (MAD)	0.3197	0.3391
Mean absolute percent error (MAPE)	1.0362	1.0619

*Note: Statistics were derived from a 2-node optimal tree configuration using 10-fold cross-validation to assess model stability. RMSE and MAD are expressed in mg KOH/g

The relative variable importance analysis identifies the iodine value (IV) as the primary determinant for predicting the acid value in polyoxyl 40 hydrogenated castor oil; achieving a maximum importance score of 100.0% (Figure

actual laboratory results. While the dashed 45-degree line represents an ideal 1:1 correlation; the concentration of data points in the lower-left and upper-right quadrants confirms that the model captures the primary variance in the dataset.

The presence of some outliers, particularly batches with actual acid values exceeding 1.5 that were fitted at the 0.97 mean, indicates that while the tree is highly effective at identifying the "quality tier" of a batch, latent variables not included in the model may account for the extreme upper-range fluctuations. Analysis of the extreme outliers in Terminal Node 2 (AV > 1.5) suggests a compounding effect of multiple risk factors. While the model's primary split is based on an iodine value > 0.45, these specific batches frequently coincide with the upper quartiles of water content. This indicates that while unsaturation provides chemical susceptibility, high moisture acts as the primary driver for the accelerated ester hydrolysis required to reach such high acid values. Although storage duration was not a measured parameter in this study, the presence of these outliers underscores the need to control both saturation levels and moisture ingress to prevent extreme quality deviations. Overall, the consistent clustering seen in the test panel validates the robustness of the 10-fold cross-validation approach and supports the use of this predictive framework as a reliable industrial screening tool.

Optimized production analysis

Polyoxyl 40 hydrogenated castor oil

The CART model offers key, actionable insights for production teams to optimize manufacturing (Garuti and Mu, 2025):Critical Quality Thresholds:To ensure a stable low acid value (~0.26); quality control protocols should prioritize maintaining the iodine value at or below a threshold of 0.45. This serves as a primary indicator of product stability. Troubleshooting High Acidity:If batch testing reveals an acid value exceeding 0.90; the model indicates that troubleshooting efforts should prioritize evaluating the iodine value and water content, rather than simply adjusting the processing temperature (TempTur). Proactive Monitoring and Resource Allocation: Because ROI and congealing time (CongT) show minimal impact (<3.0% importance) on acidity; monitoring resources should be focused primarily on moisture levels and saturation control to prevent quality issues. Process Consistency and Reduced Variance: Maintaining process parameters within the defined "Node 1" thresholds ensures consistent output; reducing process variance and preventing anomalies in production data; adhering to a robust; consistent operating philosophy.

This research significantly advances the Quality by Design (QbD) paradigm by transitioning from reactive batch testing to proactive quality assurance. By identifying the iodine value (IV) as a critical material Attribute (CMA) with a definitive threshold of ≤ 0.45, the study establishes a scientifically derived operating window that ensures the stability of the acid value—a primary critical quality attribute (CQA). The implementation of CART® modeling allows for the creation of a robust "design space," where complex, non-linear interactions of chemical properties are distilled into actionable decision rules. This predictive approach

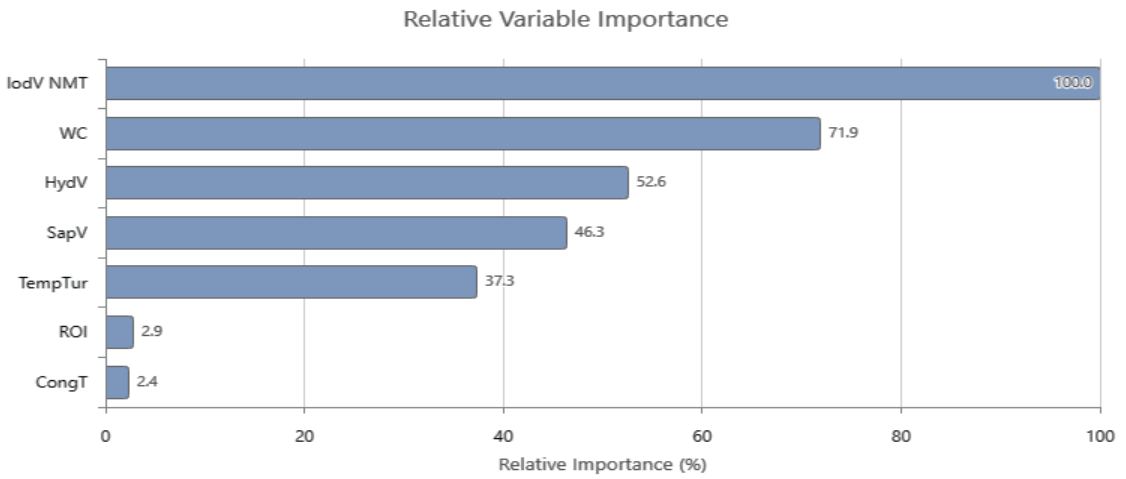

Fig. 3. Relative variable importance chart. A bar chart ranking predictors from 100% to 0% based on their influence on the model's predictive accuracy

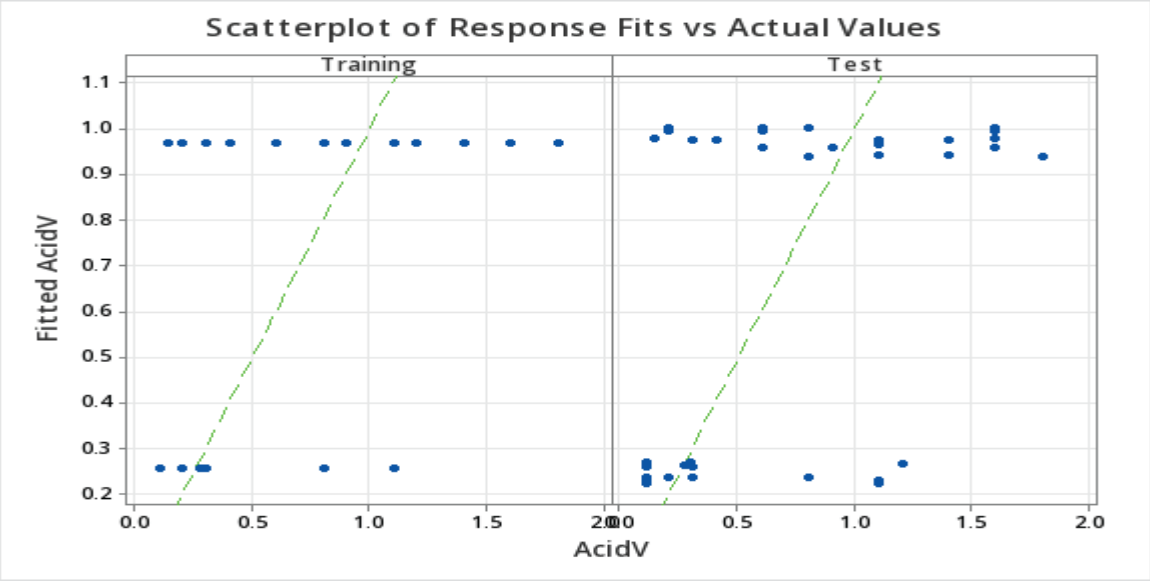

Fig. 4. Scatterplot of Response Fits vs. actual values. A diagnostic plot comparing the predicted AV against the laboratory-measured values (units in mg KOH/g) for both training and test datasets

enables manufacturers to adopt a consistent " Predictive Control Strategy" for quality, ensuring that batches are designed to meet specifications through upstream parameter control rather than downstream rejection. Ultimately, this methodology enhances process capability and provides a transparent, data-driven foundation for continuous quality improvement in excipient manufacturing.

Conclusion

This research validates the application of CART® modeling as a high-precision tool for ensuring the chemical consistency of polyoxyl 40 hydrogenated castor oil (PHCO). By analyzing 48 industrial batches under USP-standardized protocols, the model identified iodine value (IV) as the primary determinant of product stability, possessing a relative importance of 100%. A critical non-linear threshold was established at IV $\leq$ 0.45; batches within this limit maintained a superior mean acid value of 0.256, whereas those exceeding it demonstrated significantly higher acidity (0.968). Secondary analysis highlighted water content (71.9%) and hydroxyl value (52.6%) as significant predictors, while physical markers like congealing temperature proved negligible. These findings provide a structured roadmap for process optimization, shifting quality control from broad monitoring to targeted risk management of saturation and moisture levels.

The 10-fold cross-validation confirms the model's reliability, offering a robust " Predictive Control Strategy" for consistent batch production. Implementing these data-driven decision rules allows manufacturers to proactively mitigate the risk of out-of-specification results, enhancing supply chain transparency and ensuring the functional reliability of PHCO in complex pharmaceutical formulations. This methodology serves as a reproducible framework for digitalizing quality assurance in excipient manufacturing.

Furthermore, the CART® methodology presented in this study is not limited to PHCO; it provides a versatile and reproducible framework that can be adapted for other complex non-ionic surfactants, such as Polysorbate 80 or various Macrogols. By integrating the specific critical quality attributes of these materials as model predictors, this data-driven approach can be utilized to establish similar predictive decision rules, ensuring consistent batch-to-batch stability and performance across a wider range of industrial excipients.

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