

Central composite design optimisation of the alkylphenol-based detergent additive characteristics

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Abstract

In this study, the alkylphenol-based detergent-dispersant additive AKI-150 is optimised theoretically and experimentally using response surface methodology with a central composite design (CCD). Alkylphenol is condensed with formaldehyde and glycine in two stages to create this additive, which is then neutralised and carbonated using calcium hydroxide and carbon dioxide. By stabilising finely distributed calcium carbonate, the additive acts as a high-alkaline detergent, effectively neutralising acidic by-products produced during combustion in an engine. To maximise total base number (TBN) while minimising corrosiveness and maintaining acceptable viscosity, four important reaction variables were chosen for statistical optimisation: formaldehyde mass, glycine mass, $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio and carbonation stage temperature. Design-Expert software was used to analyse a 30-run face-centered CCD comprising 18 experimental observations and 12 supplementary simulated data points. The design provided broad coverage of the investigated experimental domain and enabled a comprehensive evaluation of the effects and interactions of the selected synthesis variables on TBN, viscosity and corrosiveness. The selected models showed good predictive performance, with adjusted R^2 values ranging from 0.845 to 0.971 (specifically for TBN) and predicted R^2 values ranging from 0.789 to 0.933. The findings demonstrate the efficacy of CCD-based optimisation for complex multivariable chemical systems by confirming that AKI-150 has improved alkalinity and rheology compared with traditional detergent additives.

1. Introduction

Friction, wear and lubrication interact to control tribological systems found in internal combustion engines and industrial machinery. Since frictional energy dissipation, surface deterioration and lubricant chemistry are inextricably linked, tribology, which is formally defined as the science of interacting surfaces in relative motion, must be viewed as a system-level phenomenon rather than as discrete mechanical effects [1,2]. Recent studies on lubricant additives for engine oils further

demonstrate the importance of additive chemistry in controlling lubricant performance and protecting engine components [2].

Base oils and performance additives are combined in chemically engineered formulations called lubricants to give them qualities that base oils alone cannot. Detergent-dispersant additives are crucial for neutralising acidic combustion by-products, preventing deposit formation, and preserving surface cleanliness. The total base number (TBN), which indicates the alkaline reserve available to prevent acid formation during service life, is frequently used to measure the efficacy of detergent additives [3]. One of the most popular detergent classes in lubricating oils is alkylphenol-



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based detergents. The stabilisation of finely distributed alkaline metal carbonates, usually calcium carbonate, within an organic surfactant matrix gives them their functionality. Under extreme mechanical and thermal conditions, this structure allows for long-term acid neutralisation while preserving dispersion stability [3,4]. Thus, one of the main design challenges in additive chemistry is striking a balance between alkalinity, viscosity and corrosion behaviour.

The synthesis parameters that control carbonate particle size, dispersion stability and surface activity, such as reactant ratios, carbonation temperature and neutralisation efficiency, have a significant impact on the tribological performance of overbased detergents [5]. For such multivariable systems, traditional trial-and-error optimisation techniques are ineffective and frequently miss interaction effects between synthesis parameters [6]. A methodical framework for modelling complex chemical systems with less experimental effort is provided by statistical experimental design techniques, especially response surface methodology (RSM) using central composite design (CCD). While determining the best operating regions for conflicting performance goals, CCD permits quantitative evaluation of interaction and quadratic effects [7].

AKI-150 is an alkylphenol-based detergent-dispersant additive that contains nitrogen and was created to achieve high alkalinity with regulated viscosity and corrosion behaviour. Glycine ($\text{NH}_2\text{--CH}_2\text{--COOH}$) is used in this system as the nitrogen donor during condensation, introducing bifunctional amine-carboxyl groups that affect surface activity and carbonate stabilisation [8,9]. The present study focuses on the combined effects of reactant composition and carbonation conditions on TBN, viscosity and corrosiveness in the synthesis of AKI-150 using CCD-based optimisation.

2. Methodology

RSM was chosen as the main optimisation approach because it effectively models non-linear chemical reactions in which variables interact and quadratic effects are present. Among various RSM designs, a face-centered CCD was selected for its efficiency in estimating second-order polynomial models while keeping all experiments within realistic chemical boundaries [7,10]. CCD is especially useful for additive synthesis, where straying too far beyond the feasible chemical range can cause unstable reactions, incomplete

neutralisation or unrealistic products. With its face-centered setup, all axial points remain within the factor boundaries, ensuring chemical relevance for every design point [10,11]. A face-centered CCD was developed using Design-Expert software. The final design comprised 30 runs, including 18 experimental observations and 12 supplementary simulated data points, consisting of factorial, axial and centre runs. Model adequacy was assessed using analysis of variance, the coefficient of determination (R^2), adjusted R^2 , predicted R^2 and diagnostic plots.

Three key response variables were selected to represent the main characteristics of AKI-150: TBN (mgKOH/g), which measures the alkaline reserve and acid-neutralisation capacity, kinematic viscosity (mm^2/s), which characterises the flow behaviour and dispersion stability of the additive and corrosiveness (g/m^2), reflecting its potential to cause metal degradation. Since these responses often compete, a desirability-based multi-response optimisation was used. Each variable had its own desirability function, prioritising TBN maximisation while keeping viscosity and corrosiveness within acceptable limits. The overall desirability was calculated as the geometric mean of the individual desirabilities, enabling identification of a global optimum that satisfies all targets at once [12].

A two-stage reaction sequence comprising condensation, neutralisation and carbonation was used to synthesise AKI-150, as schematically illustrated in Figure 1. In the first stage, alkylphenol condenses with formaldehyde and glycine to form a nitrogen-containing intermediate. Calcium hydroxide and carbon dioxide are then used to neutralise and carbonate this intermediate product, forming a finely distributed calcium carbonate structure that is stabilised by the organic matrix [8,9].

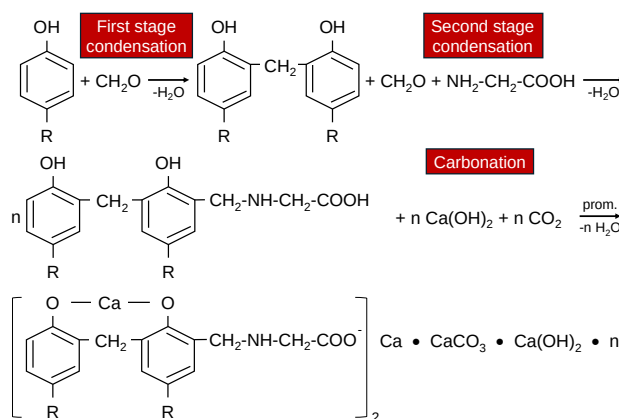


Figure 1. Reaction scheme for the two-stage synthesis, neutralisation and carbonation of AKI-150

Alkylphenol was used as the base reactant at a fixed amount of 100 g, while the amounts of formaldehyde and glycine were varied according to the CCD matrix. In the design, formaldehyde was investigated over the range of 15–30 g and glycine over the range of 6–8 g. After the condensation stages, calcium hydroxide and carbon dioxide were introduced for neutralisation and carbonation, with the mole ratio varied from 1.70 to 2.05 and the carbonation stage temperature varied from 80 to 85 °C, according to the experimental design. Based on previous experimental investigations, the temperature for the initial condensation stage (approximately 75 °C) was set at its previously established optimal value [5,9] to simplify the optimisation process and was not included as an optimisation factor. This temperature was selected to provide a controlled condensation stage for the formation of the Mannich-type intermediate, while avoiding the introduction of an additional process variable that could increase the experimental domain without being the primary focus of the present optimisation. The CCD was therefore designed around four variables considered most relevant to additive performance: formaldehyde mass, glycine mass, calcium hydroxide / carbon dioxide mole ratio and carbonation stage temperature. Their experimental values are presented in Table 1.

The synthesised products were characterised by TBN, kinematic viscosity and corrosiveness. TBN was determined according to ASTM D2896, kinematic viscosity was determined using a rotary viscometer according to GOST 26581-85 and corrosiveness was evaluated by the weight loss method in accordance with GOST 9.054-75 (Method 1). The ranges of the four independent variables were selected based on preliminary experimental work and the chemical behaviour of the synthesis system. The formaldehyde and glycine ranges were chosen to provide sufficient variation during the condensation stage while avoiding excessive amounts that could negatively affect the properties of the additive. The calcium hydroxide / carbon dioxide mole ratio range was

selected to ensure effective neutralisation and carbonation without promoting excessive carbonate formation. Similarly, the carbonation stage temperature range was chosen to provide effective carbonation while avoiding excessive condensation and deterioration of dispersion stability. These ranges therefore provided practical experimental values for the CCD optimisation.

3. Results and discussion

The adequacy of the developed response models was evaluated using ANOVA and corresponding statistical parameters. Quadratic, 2FI and linear models were selected for TBN, corrosivity and viscosity, respectively, based on sequential model comparison and model adequacy statistics. The models were significant at p-value < 0.0001, with R^2 values of 0.9852, 0.9108 and 0.8666 for TBN, corrosivity and viscosity, respectively. The corresponding adjusted R^2 values were 0.9714, 0.8639 and 0.8452, while the predicted R^2 values were 0.9331, 0.7894 and 0.7961. The ANOVA table (Table 2) for TBN is provided for further reference. The quadratic model was statistically significant (F-value = 71.39, p-value < 0.0001), while the lack-of-fit was not significant (p-value = 0.5866), indicating an adequate fit of the model to the experimental TBN data.

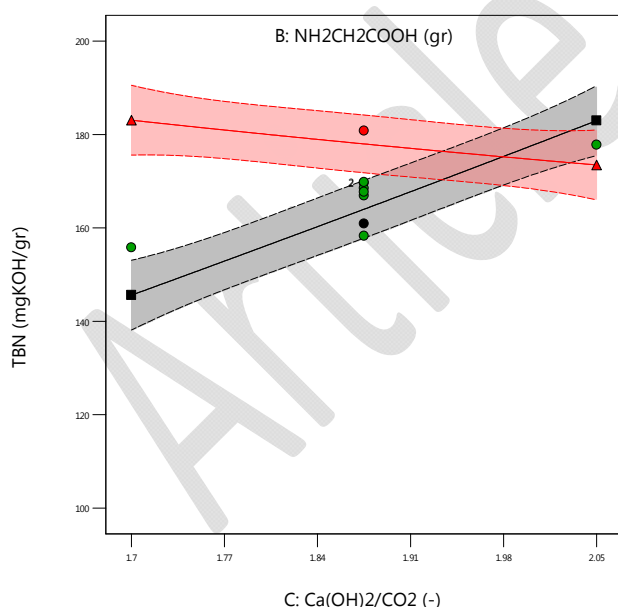
Both two-dimensional (2D) and three-dimensional (3D) response surface plots are presented in this study because they provide complementary information. The 2D contour plots facilitate the identification and interpretation of response regions and optimum ranges, while the 3D plots provide a more comprehensive visualisation of the response surface and interactions between the investigated variables. Figure 2 illustrates the interaction between glycine ($\text{NH}_2\text{CH}_2\text{COOH}$) mass and the $\text{Ca}(\text{OH})_2/\text{CO}_2$ mole ratio on TBN. The fitted lines represent the predicted TBN response at different $\text{NH}_2\text{CH}_2\text{COOH}$ amounts, while the corresponding symbols indicate the design points and the shaded areas represent the 95 % confidence bands of the fitted responses.

Table 1. Independent variables and experimental values used in the CCD

Symbol	Description	Unit	Experimental values		
A: CH_2O	formaldehyde mass	g	15.0	22.5	30.0
B: $\text{NH}_2\text{CH}_2\text{COOH}$	glycine mass	g	6	7	8
C: $\text{Ca}(\text{OH})_2/\text{CO}_2$	calcium hydroxide / carbon dioxide mole ratio	mol/mol	1.700	1.875	2.050
D: Carbonation T	carbonation stage temperature	°C	80.0	82.5	85.0

Table 2. ANOVA for quadratic model of TBN – main response parameter of CCD

Source	Sum of squares	Degree of freedom	Mean square	F-value	p-value	Status
Model	17,321.15	14	1237.23	71.39	< 0.0001	significant
A	4044.00	1	4044.00	233.35	< 0.0001	
B	880.60	1	880.60	50.81	< 0.0001	
C	868.06	1	868.06	50.09	< 0.0001	
D	25.92	1	25.92	1.50	0.2402	
A×B	2657.40	1	2657.40	153.34	< 0.0001	
A×C	56.25	1	56.25	3.25	0.0917	
A×D	1207.56	1	1207.56	69.68	< 0.0001	
B×C	2204.30	1	2204.30	127.19	< 0.0001	
B×D	888.04	1	888.04	51.24	< 0.0001	
C×D	109.20	1	109.20	6.30	0.0240	
A×A	1324.77	1	1324.77	76.44	< 0.0001	
B×B	48.75	1	48.75	2.81	0.1142	
C×C	0.2145	1	0.2145	0.0124	0.9129	
D×D	123.79	1	123.79	7.14	0.0174	
Residual error	259.95	15	17.33			
Lack-of-fit	167.15	10	16.72	0.9006	0.5866	non-significant
Pure error	92.80	5	18.56			
Corrected total	17,581.10	29				

**Figure 2.** Multivariable analysis of $\text{NH}_2\text{CH}_2\text{COOH}$ mass and $\text{Ca}(\text{OH})_2/\text{CO}_2$ mole ratio impact on TBN (A = 22.5 g and D = 82.5 °C)

At lower $\text{NH}_2\text{CH}_2\text{COOH}$ amounts, increasing the $\text{Ca}(\text{OH})_2/\text{CO}_2$ mole ratio resulted in a clear increase in TBN, whereas at higher glycine amounts the effect of the ratio became less pronounced. The higher TBN values noticed at increased

$\text{NH}_2\text{CH}_2\text{COOH}$ amounts indicate that an appropriate balance between nitrogen incorporation and carbonation conditions is required to achieve high alkalinity, rather than maximising either variable independently.

The effect of formaldehyde (CH_2O) amount and the $\text{Ca}(\text{OH})_2/\text{CO}_2$ mole ratio on the kinematic viscosity of the additive is presented in Figure 3. The response surface plot indicates that viscosity generally increased with increasing CH_2O amount, while the effect of the $\text{Ca}(\text{OH})_2/\text{CO}_2$ mole ratio was comparatively less significant within the investigated range. This behaviour is consistent with the role of CH_2O in the condensation stage, where its increased availability can promote the formation of a more extensively condensed organic structure and consequently increase viscosity [13,14]. The results therefore indicate that controlling CH_2O mass is important for achieving the required viscosity while maintaining the desired overall additive performance. The colour scale in Figure 3 and other 3D plots represents the predicted response, while the red and pink symbols indicate design points located above and below the fitted response surface, respectively.

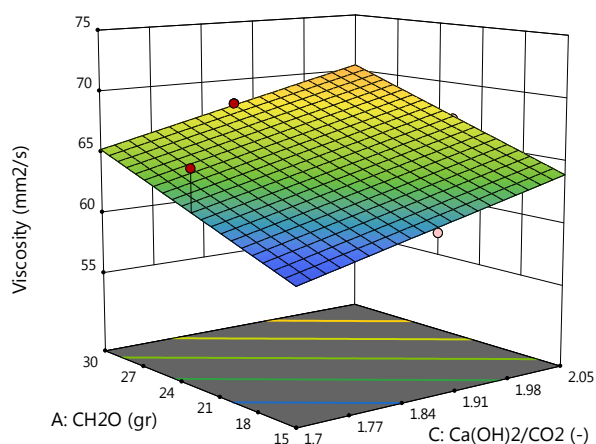


Figure 3. Impact of CH_2O mass and $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio on kinematic viscosity (B = 7 g and D = 82.5 °C)

The carbonation stage temperature (Carbonation T) showed a considerable non-linear effect on the investigated responses, as presented in Figures 4 and 5. The response surface plots indicate that increasing the temperature initially improved the response characteristics, followed by a decrease or less favourable behaviour at higher temperatures. This indicates the existence of an intermediate temperature region in which carbonation proceeds more effectively while maintaining favourable additive properties. Within the investigated range, a carbonation stage temperature of approximately 83 – 84 °C provided a favourable balance among the evaluated responses, supporting its selection as an important process variable in the optimisation. The technical statements from this study were found to be adequate compared with the literature [15,16].

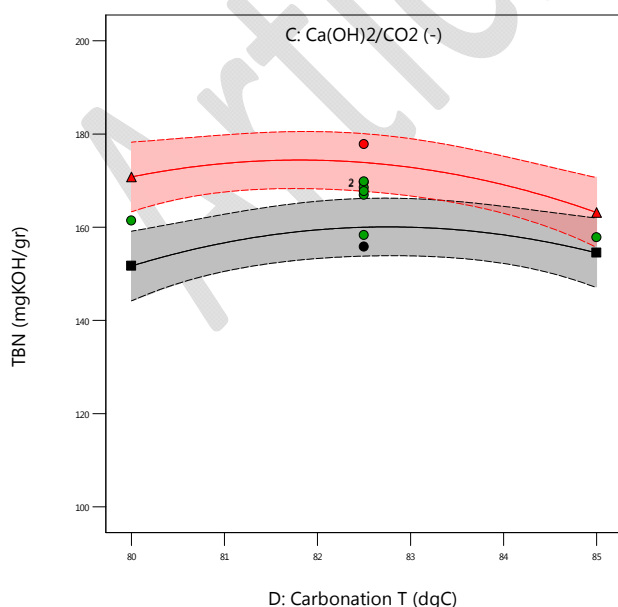


Figure 4. Multivariable analysis of carbonation stage temperature and $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio impact on TBN (A = 22.5 g and B = 7 g)

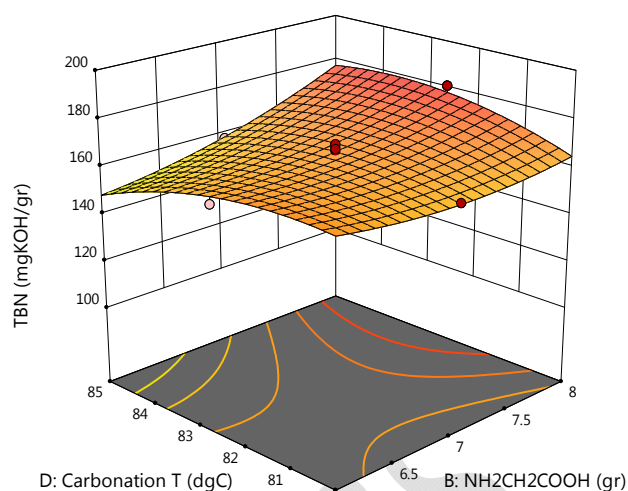


Figure 5. Impact of carbonation stage temperature and $\text{NH}_2\text{CH}_2\text{COOH}$ mass on TBN (A = 22.5 g and C = 1.875 mol/mol)

Corrosivity was also strongly influenced by the synthesis conditions, particularly glycine ($\text{NH}_2\text{CH}_2\text{COOH}$) mass and carbonation stage temperature, as presented in Figures 6 and 7. The response surface plot in Figure 6 indicates that increasing $\text{NH}_2\text{CH}_2\text{COOH}$ mass generally reduced corrosivity within the investigated range, although the effect was dependent on the $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio. This suggests that an appropriate $\text{NH}_2\text{CH}_2\text{COOH}$ level improves corrosion resistance, which is consistent with the potential surface-interaction and stabilising role of the amino-containing component [17,18].

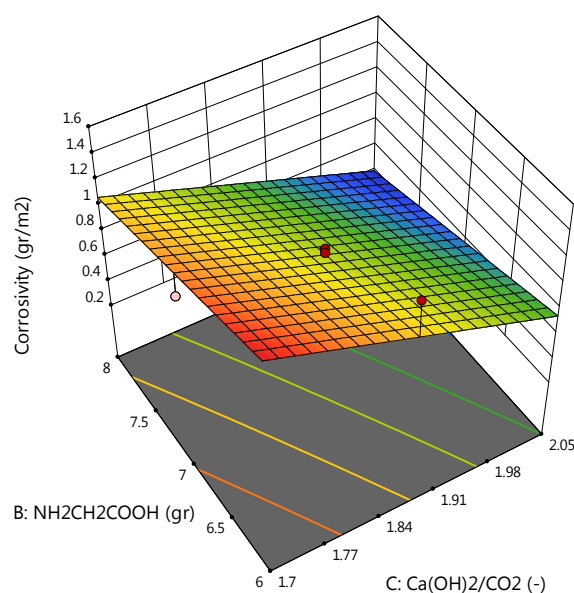


Figure 6. Impact of $\text{NH}_2\text{CH}_2\text{COOH}$ mass and $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio on corrosivity (A = 22.5 g and D = 82.5 °C)

Carbonation stage temperature also affected corrosivity, with the response surface plot in Figure

7 showing a distinct temperature-dependent trend. The results indicate that controlled carbonation conditions are important for achieving low corrosivity while maintaining the desired properties of the additive [19].

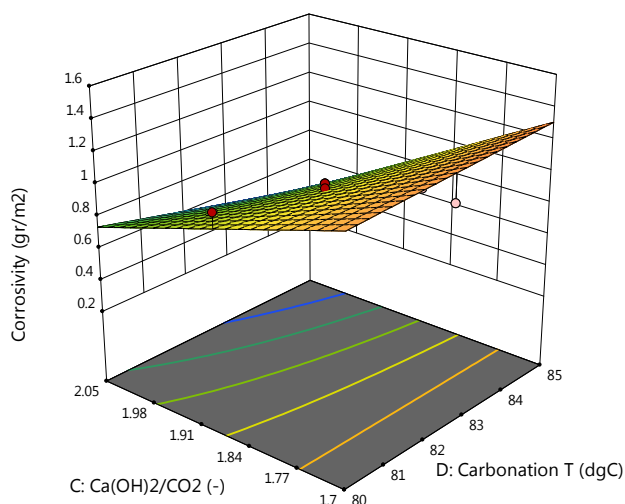


Figure 7. Impact of carbonation stage temperature and $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio on corrosivity (A = 22.5 g and B = 7 g)

Multi-response optimisation identified the optimum synthesis conditions as 29.89 g CH_2O , 7.91 g $\text{NH}_2\text{CH}_2\text{COOH}$, a $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio of 1.92 and a carbonation stage temperature of 85.0 °C. Under these conditions, the model predicted a TBN of 169 mg KOH/g, a corrosivity of 0.547 g/m² and a kinematic viscosity of 69.25 mm²/s, with an overall desirability of 0.873. All optimised factor values were within the investigated experimental ranges, confirming that the selected solution did not require extrapolation beyond the experimental domain.

4. Conclusions

This study demonstrates the applicability of central composite design combined with response surface methodology for optimising the synthesis of the glycine-modified alkylphenol-based detergent-dispersant additive AKI-150. This approach enabled simultaneous evaluation of the effects of reactant composition and carbonation conditions on total base number, kinematic viscosity, and corrosiveness, and their use for multi-response optimisation.

The results showed that glycine amount, $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio, and carbonation stage temperature were important factors affecting the additive's characteristics. Glycine plays a dual role in the system by introducing nitrogen during

condensation and contributing to surface activity and carbonate stabilisation. The results indicate that its amount must therefore be balanced rather than simply maximised. Similarly, the $\text{Ca(OH)}_2/\text{CO}_2$ mole ratio and carbonation stage temperature strongly influenced the formation and stabilisation of the carbonate phase, which in turn affected alkalinity, viscosity and corrosion behaviour.

References

- [1] E. Tsakiridis, P. Nikolakopoulos, Fullerene oil tribology in compression piston rings under thermal considerations, *Lubricants*, Vol. 11, No. 12, 2023, Paper 505, DOI: [10.3390/lubricants11120505](https://doi.org/10.3390/lubricants11120505)
- [2] A. Peskovets, N. Semenov, N. Pugachev, Transition metal dithiophosphates as antioxidant additives for engine oils, *Tribology and Materials*, Vol. 5, No. 2, 2026, pp. 74-80, DOI: [10.46793/tribomat.2026.011](https://doi.org/10.46793/tribomat.2026.011)
- [3] M. Torbacke, Å. Kassman Rudolphi, E. Kassfeldt, *Lubricants: Introduction to Properties and Performance*, John Wiley & Sons, Chichester, 2014, DOI: [10.1002/9781118799734](https://doi.org/10.1002/9781118799734)
- [4] D. Xia, Y. Wang, H. Liu, J. Yan, H. Lin, S. Han, Research progress of antioxidant additives for lubricating oils, *Lubricants*, Vol. 12, No. 4, 2024, Paper 115, DOI: [10.3390/lubricants12040115](https://doi.org/10.3390/lubricants12040115)
- [5] R. Gasimov, V. Farzaliyev, E. Naghiyeva, R. Mammadova, S. Nasirova, Mathematical modelling and optimization of alkyl-phenol based additive – AKI-56 for motor oils: A full factorial design approach, *Nature & Science*, Vol. 7, No. 6, 2025, pp. 20-26, DOI: [10.36719/2707-1146/57/20-26](https://doi.org/10.36719/2707-1146/57/20-26)
- [6] A.K. Mamedova, V.M. Farzaliev, A.K. Kyazimzade, New sulfur-, nitrogen-, and boron-containing multifunctional alkylphenolate additives for motor oils, *Petroleum Chemistry*, Vol. 57, No. 8, 2017, pp. 718-721, DOI: [10.1134/S0965544117080072](https://doi.org/10.1134/S0965544117080072)
- [7] A. Reza, L. Chen, X. Mao, Response surface methodology for process optimization in livestock wastewater treatment: A review, *Heliyon*, Vol. 10, No. 9, 2024, Paper e30326, DOI: [10.1016/j.heliyon.2024.e30326](https://doi.org/10.1016/j.heliyon.2024.e30326)
- [8] A.K. Kazim-zadeh, E.A. Nagiyeva, A.A. Gadirov, R.A. Mammadova, B.I. Abdullayev, M.A. Mirzoyeva, Многофункциональная азотсодержащая алкилфенолятная присадка к моторным маслам [Multifunctional nitrogen containing alkylphenolate additive for motor oils], *Caspian Corrosion Control*, Vol. 1, 2019, pp. 44-47, DOI: [10.54787/cc-2710-4389-2019-00006](https://doi.org/10.54787/cc-2710-4389-2019-00006) [in Russian].

- [9] E.A. Naghiyeva, R.Z. Gasimov, A.A. Gadirov, V.M. Farzaliyev, H.A. Javadova, T.S. Ahmadov, M.A. Musayeva, M.H. Abbasov, R.A. Mammadova, S.I. Nasirova, R.Q. Heydarova, Motor yağlarına azotsaxlayan çoxfunksiyalı aşqarın alınma üsulu [Method of Obtaining Nitrogen-Containing Multifunctional Additive for Motor Oils], Patent İ 2025 0076, Intellectual Property Agency of the Republic of Azerbaijan, Baku, 2025 [in Azerbaijani].
- [10] E.W. Elsayed, M.F. Emam, Application of response surface methodology using face-centered central composite design for studying long-term stability of gliclazide-loaded multiparticulate systems, *Journal of Pharmaceutical Sciences*, Vol. 113, No. 8, 2024, pp. 2274-2285, DOI: [10.1016/j.xphs.2024.03.012](https://doi.org/10.1016/j.xphs.2024.03.012)
- [11] C.N. Njoku, S.K. Otisi, Application of central composite design with Design Expert v13 in process optimization, in P. Kayarogannam (Ed.), *Response Surface Methodology – Research Advances and Applications*, IntechOpen, London, 2023, ch. 2, DOI: [10.5772/intechopen.109704](https://doi.org/10.5772/intechopen.109704)
- [12] B. Sadhukhan, N.K. Mondal, S. Chattoraj, Optimisation using central composite design (CCD) and the desirability function for sorption of methylene blue from aqueous solution onto *Lemna major*, *Karbala International Journal of Modern Science*, Vol. 2, No. 3, 2016, pp. 145-155, DOI: [10.1016/j.kijoms.2016.03.005](https://doi.org/10.1016/j.kijoms.2016.03.005)
- [13] R.S. Kamal, N.S. Ahmed, A.M. Nasser, Study the efficiency of some compounds as lubricating oil additives, *Applied Petrochemical Research*, Vol. 3, No. 1-2, 2013, pp. 1-8, DOI: [10.1007/s13203-012-0020-8](https://doi.org/10.1007/s13203-012-0020-8)
- [14] O.G. Shevchenko, E.V. Buravlev, Antioxidant activity of Mannich bases derived from natural and synthetic phenols, *Russian Chemical Bulletin*, Vol. 72, No. 9, 2023, pp. 1972-1990, DOI: [10.1007/s11172-023-3991-y](https://doi.org/10.1007/s11172-023-3991-y)
- [15] Y. Guan, E. Marquis, M. Clelia Righi, J. Galipaud, F. Dubreuil, J. Dufils, E. Macron, F. Dassenoy, M.-I. de Barros Bouchet, Friction control by load-induced structure modification of overbased detergent in fully formulated lubricant, *Tribology International*, Vol. 192, 2024, Paper 109307, DOI: [10.1016/j.triboint.2024.109307](https://doi.org/10.1016/j.triboint.2024.109307)
- [16] F. Kang, D. Wang, Y. Pu, X.-F. Zeng, J.-X. Wang, J.-F. Chen, Efficient preparation of monodisperse CaCO₃ nanoparticles as overbased nanodetergents in a high-gravity rotating packed bed reactor, *Powder Technology*, Vol. 325, 2018, pp. 405-411, DOI: [10.1016/j.powtec.2017.11.036](https://doi.org/10.1016/j.powtec.2017.11.036)
- [17] A. Sahaya Raja, S. Rajendran, J. Sathiyabama, P. Angel, Corrosion control by aminoacetic acid (glycine) an overview, *International Journal of Innovative Research in Science, Engineering and Technology*, Vol. 3, No. 4, 2014, pp. 11455-11466.
- [18] N. Pramanik, R. Kumar, A. Ray, V.K. Chaudhary, S. Ghosh, Corrosion behavior of mild steel in the presence of urea, sodium chloride, potassium chloride, and glycine: A kinetic and potentiodynamic polarization study approach, *Journal of Bio- and Tribo-Corrosion*, Vol. 8, No. 4, 2022, Paper 112, DOI: [10.1007/s40735-022-00713-w](https://doi.org/10.1007/s40735-022-00713-w)
- [19] M. Zheng, G. Ren, S. Wang, Y. Li, M. Xing, Investigating the effect of overbased sulfonates on calcium sulfonate complex grease: Enhancements in physicochemical, rheological, and tribological properties, *RSC Advances*, Vol. 14, No. 45, 2024, pp. 32992-33006, DOI: [10.1039/d4ra04307c](https://doi.org/10.1039/d4ra04307c)