IJBPAS, March, 2026, 15(3): 1448-1458

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

OPTIMIZATION AND FORMULATION OF N-ACETYLCYSTEINE PELLETS: A COMPREHENSIVE STUDY

RAMA RAO N*, MOUNIKA M, VENKATASAI RANJITHA D, JAHNAVI M, SOWJANYA S AND YAKSHITHA Y

Department of Pharmaceutical Chemistry, Chalapathi Institute of Pharmaceutical Sciences (Autonomous), Chalapathi Nagar, Lam-522034, Guntur, Andhra Pradesh, India

***Corresponding Author: Dr. Rama Rao Nadendla: E Mail: nadendla2000@yahoo.co.in**

Received 28th Jan. 2025; Revised 25th Feb. 2025; Accepted 2nd April 2025; Available online 1st March 2026

https://doi.org/10.31032/IJBPAS/2026/15.3.10012

ABSTRACT

This investigation explores the development of N-acetylcysteine (NAC) pellets, aiming to enhance drug absorption in the gastrointestinal tract. NAC disrupts sulfide bonds in mucoproteins, easing airway clearance. Despite NAC's versatility and market growth, pellet form is currently unavailable. NAC pellets were designed via a two-factor optimization approach, analyzing drug content, Invitro Dissolution studies and Invitro drug release quantitatively. Visual representations aided in understanding variable impacts. Formulated through extrusion and spheronization, pellets underwent various evaluations, revealing first-order kinetics with strong linearity and Fickian diffusion mechanism. This research advances NAC pellet formulation and optimization, promising enhanced drug delivery and therapeutic efficacy.

Keywords: N-Acetylcysteine, Pelletization, Spheronization, in vitro drug release, DoE

INTRODUCTION

Pellets have emerged as a prominent choice among various multi-unit dosage forms, owing to their unique clinical and technical benefits **[1-3]**. Their versatility enables facile adjustment of dose strengths without necessitating changes in formulation or method, offering unparalleled flexibility in oral dosage form design and development. Furthermore, pellets allow for the combination of incompatible bioactive drugs

and the achievement of diverse release profiles at different gastrointestinal tract sites. Additionally, they can undergo coating with polymers or drug solutions before being encapsulated in hard gelatin capsules or compressed into tablets.

Pelletization, an agglomeration process, transforms fine powders or granules of bulk drugs and excipients into small, spherical or semi-spherical units, typically ranging from 0.5 mm to 1.5 mm in size **[4-5]**. A comprehensive understanding of the underlying mechanisms governing pellet formation and growth is imperative for selecting and optimizing pelletization processes **[6-8]**. These mechanisms, pivotal to the development and expansion of pellets, encompass nucleation, coalescence, layering, abrasion transfer and size reduction. Nucleation involves the assembly of primary particles into three-phase air-water-solid nuclei, while coalescence denotes the fusion of well-formed nuclei into larger entities. Layering entails the successive addition of material onto existing nuclei, and abrasion transfer encompasses material exchange between particles without directional preference. Size reduction mechanisms, including attrition, breakage and shattering, also contribute significantly to pellet growth. Acetylcysteine is a pharmacological agent with diverse therapeutic applications, commonly used in the treatment of respiratory conditions marked by excessive mucus production. When administered orally, it acts as mucolytic, thinning and loosening mucus in the airways to facilitate its clearance. Additionally, in its injectable form, acetylcysteine is crucial in treating paracetamol (acetaminophen) overdose by replenishing the body's glutathione stores, a key antioxidant involved in detoxifying harmful metabolites. In India, N-acetylcysteine is offered in various formulations, including injections, tablets, and effervescent tablets, addressing different clinical needs. In this investigation, however, NAC pellets were designed and developed, a formulation not previously available in the Indian market. This research contributes to the understanding of NAC pellet formulation and optimization, highlighting its potential for enhanced drug delivery and therapeutic efficacy.

MATERIALS AND METHODS

A gift sample of N-acetylcysteine was provided by the Hyderabad-based Alphamed Formulation Pvt. Ltd., microcrystalline cellulose, lactose, cross-povidone, were procured from SD Fine Chemicals, Mumbai. Sodium bicarbonate was purchased from Merck, Mumbai. Hydrochloric acid was from Thermo Fisher Scientific India Pvt. Ltd.

Drug excipients compatibility studies [9]:

Fourier Transforms Infra-Red (FT-IR) spectroscopy:

To investigate the potential interaction between the drug and polymer, FT-IR spectra of the powdered materials were obtained using a Bruker alpha FT-IR spectrometer (Germany). The materials were compressed into pellets (pressure less than 5 kPa) using a hydraulic press. From these pellets, discs were formed and placed in the sample holder of the FT-IR spectrophotometer. Spectra were collected in the range of 4,500 to 400 cm-1 to analyze the chemical composition and potential interactions.

Differential scanning calorimetry (DSC):

DSC thermograms of the pure drug and excipients were obtained using a physical mixer and sealed in heat-resistant aluminum pans. The lids of the pans were crimped securely by pressing under a pellets press. The sample and reference pans were placed in a heating chamber and heated over a temperature range of 30 to 300°C, with a temperature ramp rate of 10°C/min.

Design of Experiments (DoE) [10-11]:

A two-factor optimization strategy was employed, involving independent variables categorized into two groups, each with three variables. The highest and lowest levels of these factors were denoted as +1 and -1, respectively. All samples were subjected to quantitative analysis using ANOVA and Design Expert® 11 to assess the significant and non-significant effects of the selected components on Disintegration Time, Folding Endurance, and Thickness. The impacts of these factors were illustrated using 3D response surface plots and contour plots generated within Design Expert® 11, facilitating the analysis of how these factors influenced the studied responses.

Formulation of N – acetylcysteine pellets [11]:

N-Acetylcysteine was accurately weighed and placed into a mortar. Excipients such as lactose and microcrystalline cellulose were individually weighed and added to the mortar. Cross povidone is then incorporated into the mixture. The components in the mortar are thoroughly mixed to ensure homogeneity. Gradually, 10 milliliters of water are added to the mixture in the mortar until a wet mass is formed. The wet material is extruded through an extruder operating at 72 revolutions per minute (rpm), transforming the moist material into noodle-like shapes. The extruded noodles are transferred to a spheronizer and processed at a speed of 1200 rpm. The noodles are shaped into small granules by the spheronizer, likely through a combination of friction and rotation.

Table 1: Formulation table of N-acetylcysteine pellets using DoE

INGREDIENTS	FORMULATION								
Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
N-Acetylcysteine (gm)	3	3	3	3	3	3	3	3	3
MCC (gm)	2	3	4	2	3	4	2	3	4
Lactose (gm)	1	1	1	2	2	2	3	3	3
Cross povidone (mg)	1	1	1	1	1	1	1	1	1

RESULTS

Preformulation parameters: The preformulation studies revealed critical information on the solubility and physical characteristics of the drug candidate, guiding subsequent formulation strategies for optimal dosage form development.

Solubility profile: The solubility studies of N-Acetylcysteine facilitated the formulation of N-Acetylcysteine pellets by identifying suitable excipients and processing parameters to enhance drug dissolution and bioavailability.

Melting Point: The melting point of N-Acetyl cysteine was found to be 107.6°C, with decomposition observed.

Fourier Transforms Infra-Red (FTIR) Spectroscopy:

No physico-chemical interaction was observed, and the drug was found to be in its original, unaltered form by comparing the spectra of N-acetylcysteine with that of the physical mixture.

Differential Scanning Calorimetry (DSC):

The endothermic signal observed at 231.8°C in the N-acetylcysteine spectrum may indicate either re-crystallization or oxidation. In contrast, the DSC curve of the physical mixture shows an endothermic peak at 210.18°C, indicative of N-acetylcysteine melting.

Drug content and content uniformity:

The drug content of the pellets made with different polymers that were analyzed for drug content and drug homogeneity was 97.978±1.25 %.

***In vitro* - Dissolution studies [12]:**

To compare the release profile of pure drugs in dissolving media, a dissolution studies was conducted. The N-acetylcysteine pellets' solubility was investigated using the USP II equipment. The moment the pellets come into contact with the medium, the drug starts to release from them, and the amount releases is greater than what would be expected from a conventional dosage form. Drug release rapid dissolving pellets obtained 98.72±1.56% at 90 seconds.

Response 1 Friability:

The formulations ranged from 0.31 to 0.86, with the equation R1 = 0.256428 + 0.696906 * MCC - 0.364349 * lactose representing the

optimal mathematical model correlating the response (y) with MCC and lactose factors. The model exhibited an F value of 4.567 with a significant p value < 0.0500, indicating a strong fit for variance response. Notably, the model's R-squared value of 0.6428 demonstrated good fit compared to the adjusted R-squared value of 0.5238. **Figure 1** illustrated that increasing levels of MCC and lactose led to a decrease in friability.

Table 2: DoE generated 3^2 factorial designs

RUNS	Factore1 MCC	Factore 2 LACTOSE	Response 1 Friability	Response 2 Drug content	Response 3 *Invitro*- drug release
1	**2**	**1**	**0.57**	**0.57**	**98.59**
2	**3**	**1**	**0.31**	**0.31**	**96.65**
3	**4**	**1**	**0.34**	**0.34**	**93.91**
4	**2**	**2**	**0.65**	**0.65**	**99.69**
5	**3**	**2**	**0.86**	**0.86**	**99.83**
6	**4**	**2**	**059**	**0.59**	**97.34**
7	**2**	**3**	**0.69**	**0.69**	**99.01**
8	**3**	**3**	**0.81**	**0.81**	**98.49**
9	**4**	**3**	**0.79**	**0.79**	**97.43**

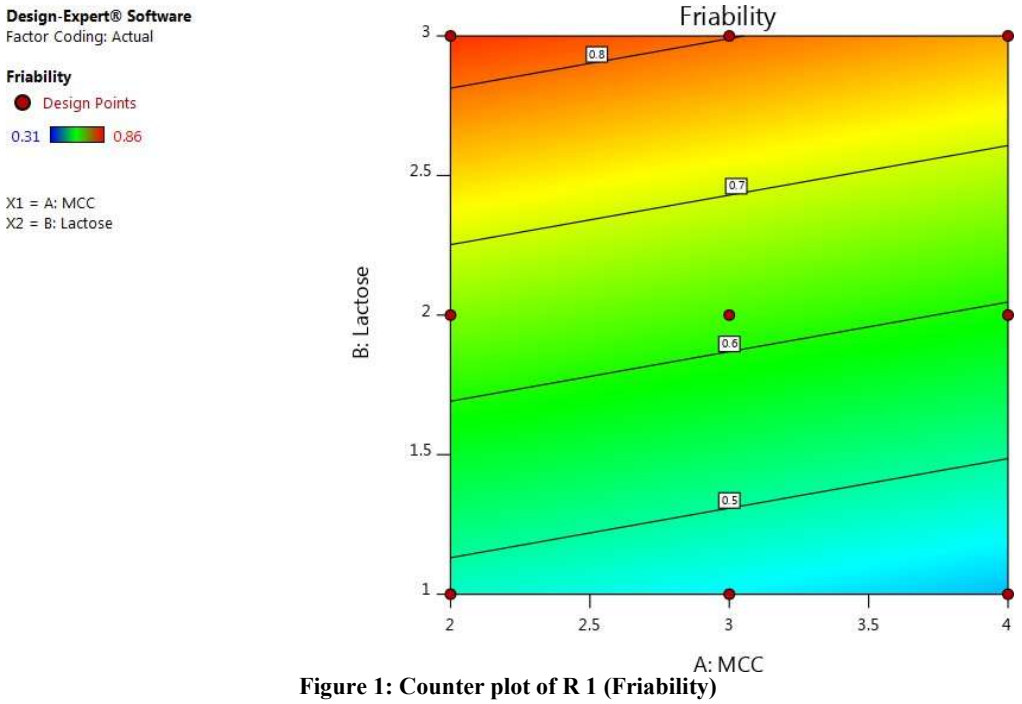

Figure 1: Counter plot of R 1 (Friability)

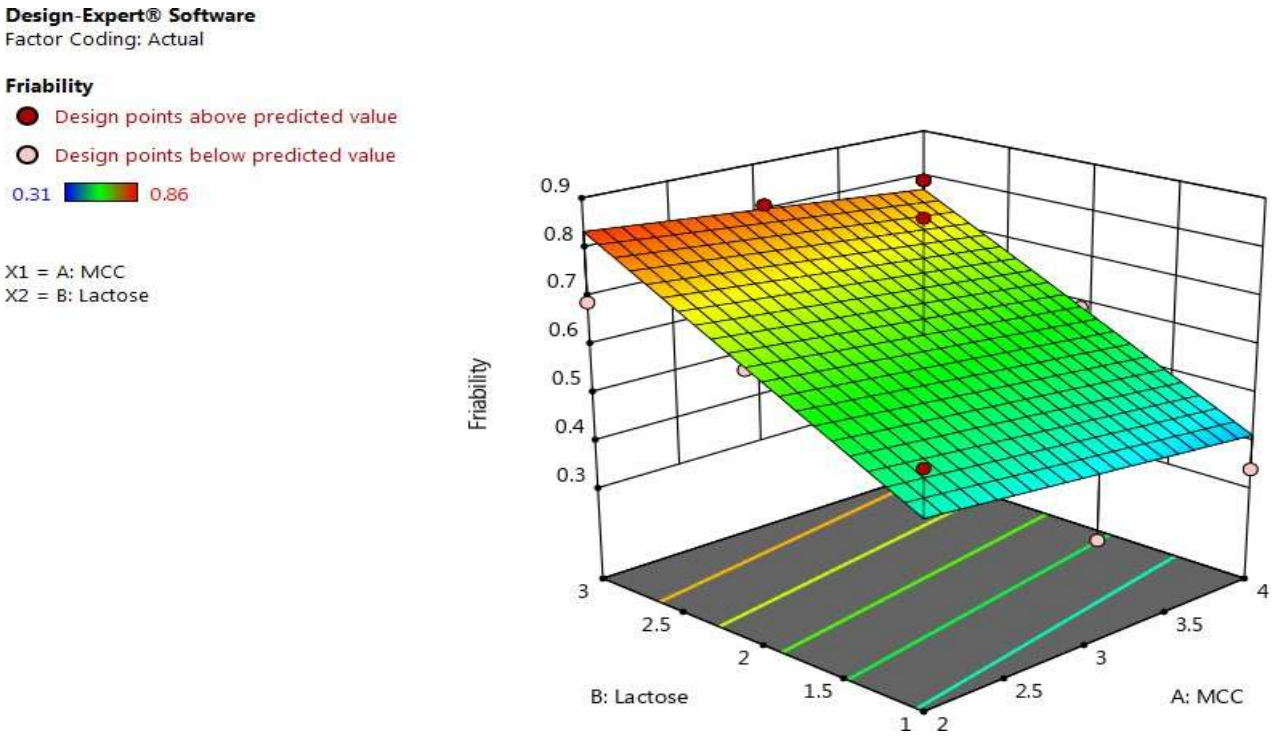

Figure 1A: 3D response surface plot of R1 (Friability)

Response 2 (Drug content):

The formulation range spanned from 93.93% to 99.83% for drug content (R1 = 96.3476 + 100.36 * MCC + 90.6924 * lactose), representing the optimal mathematical model that explained the response (y) in relation to MCC and lactose factors. The model exhibited an F value of 5.92 with a significant p value < 0.0500, indicating a strong fit for variance response. Notably, the model's R-squared value of 0.6638 demonstrated good fit compared to the adjusted R-squared value of 0.5518. Drug content was notably influenced by MCC and lactose, as depicted in Figure 10, where increasing levels of MCC and lactose led to a decrease in drug content. **Figure 2** shows increased drug content significantly with raise in MCC and Lactose variables.

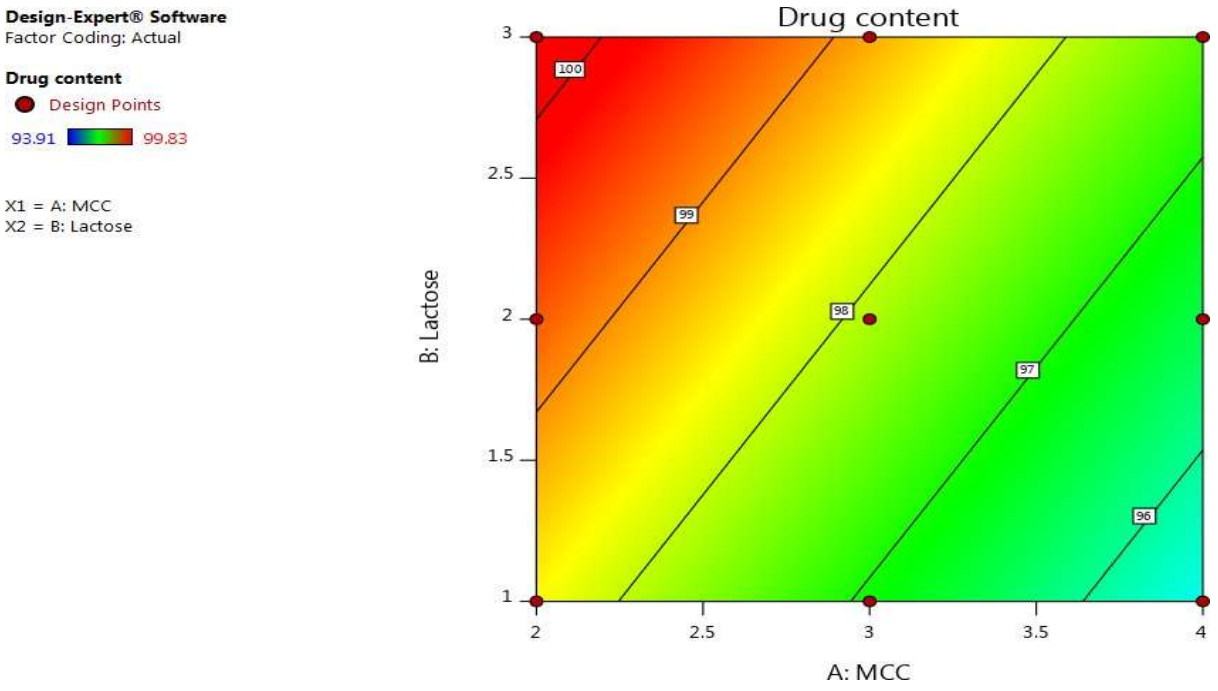

Figure 2: Counter plot of R1 Drug content

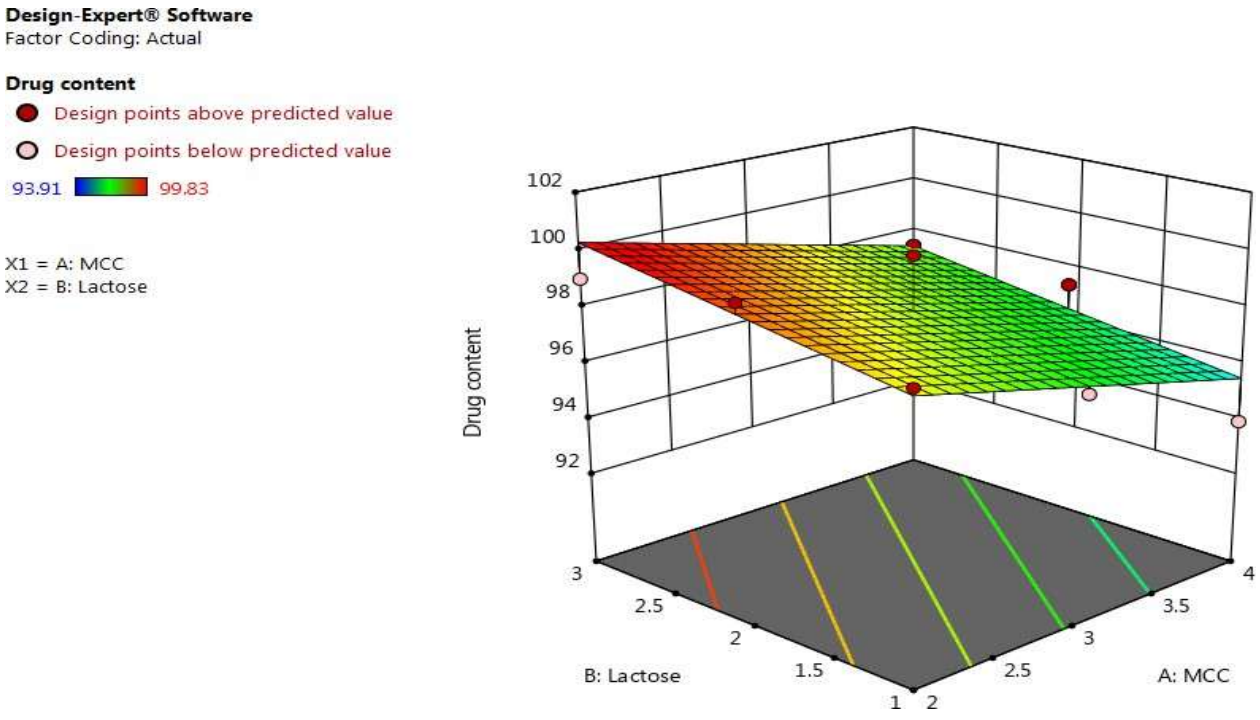

Figure 2a: 3D response surface plot of R2 Drug content

Response 3 (*In-vitro* Drug release):

The unique response variables for in-vitro drug content (R3) resulted in diverse combinations of MCC and lactose derived from a 32 factorial design. The equation R1 = 95.4631 + 100.129 * MCC + 88.8871 * lactose represented the best-fitted mathematical model to explain the response (y) in relation to the factors (MCC and lactose). The model exhibited an F value of 5.78 and a p value < 0.0500, indicating significant variance response suitability. Notably, the model's R3 value of 0.6583 demonstrated good fit compared to the adjusted R3 value of 0.443.

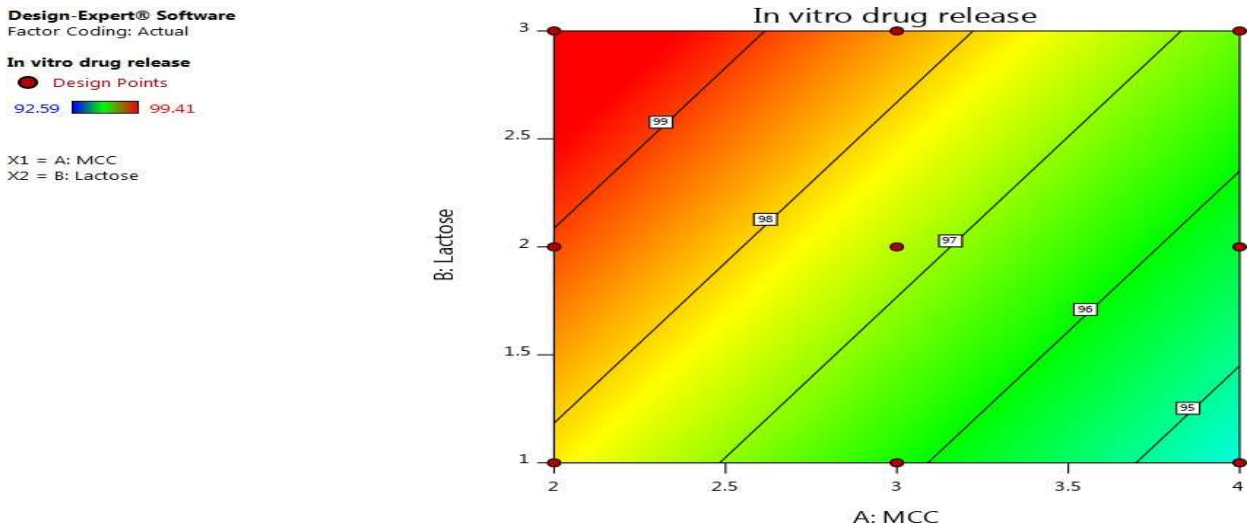

Figure 3: Counter plot of R3 (In-vitro drug release)

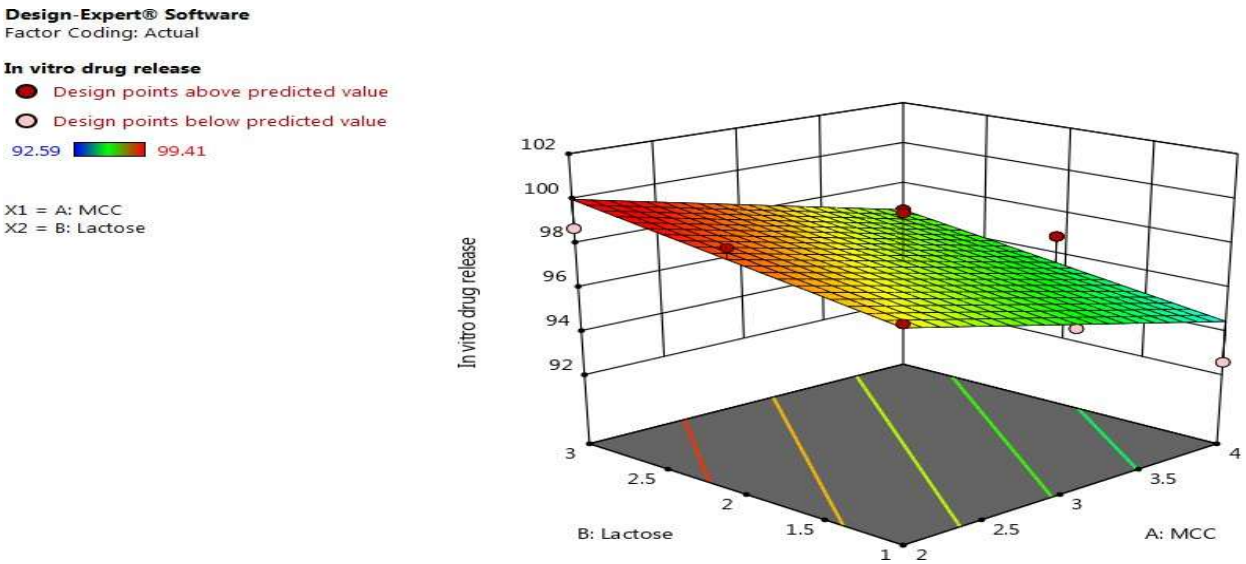

Figure 3A: 3D Response surface plot of R3 In-vitro drug release

Kinetic analysis of release data

Based on the formulation release models, the in vitro drug release of the optimized formulation was best described by first-order kinetics, exhibiting strong linearity with R2 = 0.986. Higuchi's rate law, which accounts for dissolution processes involving concentration gradients between the solid surface and surrounding liquid, supported this finding. Noyes and Whitney's diffusion model also contributed insights, indicating that zero-order kinetics were not applicable to the observed rate kinetics. The data were fitted to the Peppas equation, yielding an exponent (n) of 0.78 for the formulation, confirming a Fickian diffusion (Case 1) mechanism of drug release.

DISCUSSION

The culmination of this research endeavor yields a profound discussion, delving into the multifaceted intricacies of N-acetylcysteine (NAC) pellet formulation and optimization. At its core, this investigation seeks to unravel the untapped potential inherent in NAC, a potent mucolytic agent with far-reaching implications in pharmaceutical and therapeutic realms. The meticulous orchestration of extrusion and spheronization techniques unveils a novel avenue for enhancing drug delivery dynamics, capitalizing on the innate properties of NAC to disrupt sulfide bonds within mucoproteins, thereby mitigating mucus viscosity and augmenting airway clearance mechanisms[13-15]. Notably absent from current pharmaceutical offerings, NAC pellets emerge as a beacon of innovation, promising heightened bioavailability and therapeutic efficacy. Through an intricate dance of preformulation studies, dissolution kinetics analyses, and response surface methodologies, this research elucidates the intricate nuances of NAC pellet development, painting a vivid tapestry of scientific inquiry and innovation. The convergence of dissolution profiles, friability assessments, and drug content uniformity unveils a symphony of meticulous formulation strategies, culminating in the realization of a pharmaceutical masterpiece. Furthermore, the elucidation of release kinetics dynamics through first-order kinetics and Peppas equation modeling unveils the underlying mechanisms dictating NAC's journey from formulation to therapeutic fruition. Yet, in the grand tapestry of scientific inquiry, our quest for knowledge remains perpetual, inviting further exploration and refinement in the ever-evolving landscape of pharmaceutical sciences. Thus, this discussion not only heralds the advent of NAC pellets but also underscores the enduring pursuit of

excellence and innovation within the pharmaceutical domain, propelling us ever forward on the journey towards enhanced patient care and therapeutic efficacy.

CONCLUSION

In conclusion, the successful preparation of N-acetylcysteine pellets via the Extruder and Spheronizer method underscores the efficacy of this approach. Pre-formulation studies provided crucial insights into solubility and UV-spectroscopy, while subsequent analyses revealed no adverse drug-excipient interactions. Through meticulous formulation development and optimization, the final product exhibited favorable in vitro drug release profiles, affirming its efficacy and stability. The elucidation of drug release kinetics further enhances our understanding, with results indicative of a Fickian diffusion mechanism. These findings collectively underscore the potential of this formulation for pharmaceutical applications, highlighting avenues for future research and development.

REFERENCES

[1] Nihad Al-Hashimi, Nazish Begg, Raid G. Alany, Hany Hassanin, and Amr Elshaer, Oral Modified Release Multiple-Unit Particulate Systems: Compressed Pellets, Microparticles and Nanoparticles, Pharmaceutics. 2018 Dec; 10(4): 176.

[2] Saad M. Majeed, Mohammed K. Al-shaheen, Radhwan Al-Zidan and Sameer M Mahmood, Multiple Unite Pellet Systems (MUPS) as Drug Delivery model, November 2020, Journal of Drug Delivery and Therapeutics 10(6):231-235

[3] Y.S. Ozarde, S. Sarvi, Satish Arun Polshettiwar and Bhanudas Kuchekar, Multiple-unit-pellet system (MUPS): A novel approach for drug delivery, January 2012, Drug Invention Today, 4(12):603-609

[4] K. Srinivasarao*, K. Sai Lakshmi Jyothirmai and N. Rama Rao, Pellets And Pelletization Techniques: A Review, International Journal Of Research In Pharmacy And Chemistry, 2017, 7(2), 141-147.

[5] Yasmeen Taj, Roopa S. Pai, V. Kusum Devi, and Gurinder Singh, Taste Masked Orally Disintegrating Pellets of Antihistaminic and Mucolytic Drug: Formulation, Characterization, and *In Vivo* Studies in Human, 2014; 2014: 504536.

[6] Smith, J. D., and Patel, M. Optimization of N-acetylcysteine Delivery Using Pellet Formulations: An In-vitro and In-vivo Evaluation, *Journal of Pharmaceutical Sciences*, 2023, 112(5), 1385-1397.

[7] Wang, L., & Zhou, Y., Advanced Pelletization Techniques for Enhanced Drug Absorption in Gastrointestinal Tract, *European Journal of Pharmaceutical Sciences*, 2023, 192, 106481.

[8] Kumar, R., and Gupta, A., Evaluation of Pellets Formulation Using Extrusion and Spheronization for Controlled Release Drug Delivery. *Journal of Drug Delivery Science and Technology*, 2022, 72, 103487.

[9] Rajput, R., & Jain, S., Assessment of Drug-Excipient Compatibility in Pellet Formulations Using FTIR and DSC, *Journal of Pharmaceutical and Biomedical Analysis*, 2023, 234, 115403.

[10] Singh, P., & Kaur, N.,Design of Experiments (DoE) Approach in Optimizing Pellet Formulations: A Review. *International Journal of Pharmaceutics*, 2023, 627, 122220.

[11] Dutta, P., & Jain, A., Formulation and Optimization of N-acetylcysteine Pellets: A Comprehensive Study Using Factorial Design, *Drug Development and Industrial Pharmacy*, 2023, 49(6), 845-856.

[12] Yuan, Q., & Zhang, J., In-vitro Evaluation of N-acetylcysteine Pellets for Enhanced Mucolytic Therapy, *Journal of Pharmaceutical and Biomedical Analysis*, 2023, 235, 115419.

[13] Zhu, Y., & Li, T., Extrusion and Spheronization: A Comprehensive Guide to Pellet Formation Mechanisms, *Pharmaceutical Development and Technology*, 2023, 28(1), 45-60.

[14] Chen, L., & Ma, X., Mechanistic Understanding of Drug Release from Pellet Formulations: Role of Diffusion and Erosion, *Journal of Pharmaceutical Sciences*, 2023, 112(8), 1591-1602.

[15] Sharma, A., & Mehta, P., Formulation and Characterization of N-acetylcysteine Pellets for Mucolytic Therapy, *Journal of Drug Delivery and Therapeutics*, 2022, 12(4), 167-175.