JBP
Journal of Biochemicals and Phytomedicine
eISSN: 2958-8561

Formulation and Design of Antidiabetic Tablets from *Eucalyptus camaldulensis* Using Wet Granulation and a 2^3 Factorial Design

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ARTICLE INFO

Article Type:
Research

Article History:
Received: 30 Apr 2025
Revised: 8 Jul 2025
Accepted: 10 Jul 2025
Available online: 23 Sep 2025

Keywords:
Eucalyptus camaldulensis,
Antidiabetic agents,
Plant extracts,
Tablets,
Drug formulation,
Factorial design

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ABSTRACT

Introduction: *Eucalyptus camaldulensis*, recognized for its antidiabetic and antimicrobial properties, was formulated into an oral tablet to improve its clinical applicability. This study optimized critical formulation parameters via a 2^3 factorial design to produce tablets meeting pharmacopeial standards.

Methods: Eight formulations were prepared by wet granulation, evaluating three independent variables: binder (PVP) concentration, disintegrant (croscarmellose sodium) concentration, and kneading time. Tablets were assessed for weight variation, thickness, hardness, friability, disintegration time, and drug release in 0.1N HCl (paddle method, 75 rpm) analyzed at 258 nm.

Results: All formulations complied with standard requirements. Tablet hardness ranged from 4.42–5.42 kg, friability was <1%, and disintegration time varied between 0.55–2 minutes. Drug release at 45 minutes exceeded 91.4%, with some formulations reaching 98.8%. Factorial analysis identified optimal variable levels for quality attributes.

Conclusion: *E. camaldulensis* was successfully formulated into rapidly disintegrating tablets with high drug release, suitable for potential use in type 2 diabetes management. Further in vivo and clinical studies are warranted.

Please cite this paper as:
H Dawoud AD, Baraka Abdalla D. Formulation and design of antidiabetic tablets of *Eucalyptus camaldulensis* using wet granulation technique and 2^3 factorial design. Journal of Biochemicals and Phytomedicine. 2025; 4(2): 34-41. doi: 10.34172/jbp.2025.15.

Introduction

Diabetes mellitus continues to pose a major global health challenge, particularly in low-resource settings where access to conventional antidiabetic agents is limited and long-term therapy is often associated with adverse effects, high cost, and reduced adherence (International Diabetes Federation, 2021; American Diabetes Association, 2024). Consequently, there is growing interest in developing standardized herbal dosage forms capable of delivering safe, effective, and affordable alternatives. Transforming medicinal plant materials into solid oral dosage forms offers several advantages, including improved dose accuracy, enhanced stability, and better patient compliance; however, herbal powders often display poor flowability, inconsistent particle size, and variable compressibility, which complicate their formulation into robust tablets (Allen & Ansel, 2020).

Eucalyptus camaldulensis has gained considerable attention due to its documented antihyperglycemic, antioxidant, and anti-inflammatory activities, supported by multiple in vivo studies demonstrating reductions in blood glucose levels and favorable safety profiles (Uadia et al., 2024; Dawoud & Shayoub, 2015; Ekpe et al., 2025). In our previously published study — "Formulation and Pre-Compression Characterization of Eucalyptus camaldulensis Herbal Tablets for Antihyperglycemic Use" (J Biochem Phytomed, 2025; 4(1): 63–69) — we optimized the pre-compression characteristics of granules using a full 2^3 factorial design. The present manuscript serves as a direct continuation (Part II) of that work, shifting the focus from granule properties to the post-compression performance of the tablets, including physical strength, disintegration behavior, and dissolution efficiency. This follow-up investigation aims to determine how the key formulation factors previously studied — binder concentration, disintegrant concentration, and kneading time — influence the final tablet quality and compliance with pharmacopeial standards.

Post-compression evaluation represents a critical stage in the development of solid herbal dosage forms, as it determines whether the formulated tablets possess the mechanical integrity, disintegration profile, and dissolution behavior required for predictable therapeutic performance. Key quality attributes such as hardness, friability, disintegration time, and drug-release kinetics directly influence bioavailability and patient adherence, and they are highly sensitive to variations in formulation parameters and processing conditions (Qiu et al., 2016; Aulton & Taylor, 2021). Unlike conventional synthetic drugs, herbal tablets present additional challenges due to the intrinsic variability of plant-derived constituents, which may alter compressibility, binding behavior, and matrix robustness. Therefore, understanding how formulation factors interact to affect post-compression characteristics is essential for ensuring consistent product quality, safety, and regulatory compliance—particularly in the context of developing standardized antihyperglycemic herbal tablets that must meet pharmacopeial specifications.

Despite the promising outcomes of our previous work on optimizing the pre-compression properties of Eucalyptus camaldulensis granules, the impact of the same critical formulation factors binder concentration, disintegrant concentration, and kneading time—on the final tablet performance has not yet been systematically evaluated. This represents a significant gap in the development of standardized herbal antidiabetic tablets, as post-compression characteristics ultimately determine the product's suitability for patient use and its compliance with pharmacopeial quality requirements. Therefore, the present study aims to comprehensively assess how these formulation variables influence the mechanical strength, disintegration behavior, and dissolution efficiency of E. camaldulensis tablets prepared via wet granulation using a full 2^3 factorial design. By integrating experimental data with statistical analysis, this work seeks to identify the optimal formulation conditions necessary for producing robust, effective, and reproducible herbal tablets intended for antihyperglycemic therapy.

Materials and Methods

Leaves of *E. camaldulensis* were collected in August 2022 from the Forest Research Center in Khartoum, Sudan. The plant was authenticated by Prof. Mohammed El-Mokhtar and Prof. Dawoud H. Dawoud (Agricultural Research Corporation, Federal Ministry of Agriculture and Irrigation). The leaves were cleaned, shade-dried, and pulverized to a fine powder using a mechanical grinder. The powder passed through a 120-mesh sieve (150 µm) to ensure uniformity.

Formulation Design Using 2^3 Full Factorial Design

A 2^3 full factorial design was employed to evaluate

the effect of three independent variables: binder concentration (X_1: polyvinylpyrrolidone), disintegrant concentration (X_2: croscarmellose sodium), and kneading time (X_3). Each factor was tested at two levels (low and high), yielding eight experimental formulations (F1 to F8).

Factor levels were coded as −1 (low) and +1 (high) (Table 1).

Experimental trials were performed at all 8 possible combinations (Table 2; Mangesh et al., 2013).

Preparation of Granules

Wet Granulation Method

Tablets containing 300 mg of E. camaldulensis leaf powder were prepared using wet granulation. All ingredients (except magnesium stearate and half of the disintegrant) were sieved and dry-mixed for 10 min. The active ingredient (55% w/w of total tablet weight) was incorporated, and mixing continued for 15 min.

A granulating fluid (distilled water, 30 mL/50 g) was gradually added and blended using a porcelain mortar and pestle. The wet mass was passed through a 20-mesh sieve (850 µm) and dried at 45 ± 5 °C overnight. The dried granules were then blended with the remaining disintegrant and magnesium stearate before compression.

Tablet Compression

Granules were compressed using a single-punch tableting machine (Korsch, Erweka, Germany) with 9 mm flat-faced punches. The final tablet weight was 300 mg.

Post-Compression Evaluation

Weight Variation

20 tablets per batch were individually weighed. Tablets met USP limits if no more than 2 tablets deviated from the mean by ±7.5% and none exceeded twice that limit (Sree Giri Prasad et al., 2012).

Table 1: Low and high levels for each of the variable factors for 2^3 full factorial design

Factor No.	Variable factors	Low Level (-1)	High level (+1)
Factor1- (X1)	Amount of Binder - P.V.P	2% (W /W)	4% (W /W)
Factor2-(X2)	Amountof Disintegrant-Croscarmellose sodium	2% (W /W)	4% (W /W)
Factor3- (X3)	kneading time	6 Minutes	12 minutes

Table 2: Formulation characteristics of 2^3 full factorial design

Batch Code	Ingredients (%/tablet)						
	P.V.P	Croscarmellose sodium	*E.camaldulensis* powdered leaves	Magnesium Stearate	Lactose monohydrate	Maize starch	Quantity Tablet (%)
F1	4	4	55	0.5	24.3	12.2	100
F2	2	4	55	0.5	25.6	12.9	100
F3	4	4	55	0.5	24.3	12.2	100
F4	2	4	55	0.5	25.6	12.9	100
F5	2	2	55	0.5	27	13.5	100
F6	4	2	55	0.5	25.6	12.9	100
F7	4	2	55	0.5	25.6	12.9	100
F8	2	2	55	0.5	27	13.5	100

Table 3: Percentage composition of *E. camaldulensis* 300mg tablets

Run		Coded values			Actual values		
	formula	X1	X2	X3	X1 Binder conc%	X2 Disint. Conc.%	X3 Kneading time Minute
1	F1	+1	+1	+1	4	4	12.00
2	F2	- 1	+1	-1	2	4	6.00
3	F3	+1	+1	- 1	4	4	6.00
4	F4	- 1	+1	+1	2	4	12.00
5	F5	-1	- 1	+1	2	2	12.00
6	F6	+1	-1	+1	4	2	12.00
7	F7	+1	-1	-1	4	2	6.00
8	F8	- 1	-1	- 1	2	2	6.00

The starch and lactose were used as filer to complete the weight of tablet in ratio of 1:2 to each other's.

Thickness and Diameter

Measured using digital vernier calipers on 10 randomLy selected tablets. Results were expressed in millimeters (mm) (Cheng et al., 2000).

Hardness

Measured for 10 tablets using a Caleva hardness tester. Results were expressed in kilograms (kg) (Cheng et al., 2000).

Friability

10 tablets were weighed (W_1), tumbled at 100 rotations in a Roche friabilator, de-dusted, and reweighed (W_2). Friability (%) = $(W_1 - W_2)/W_1 \times 100$. Values <1% were considered acceptable.

Disintegration Time

Six tablets per batch were tested in purified water (900 mL, 37 ± 2 °C) using an Erweka disintegration apparatus. Time until complete disintegration was recorded (Erweka ZT-2 Huesnstanm, Germany) (Block and Yu, 2001).

Dissolution Test

Conducted in 0.1N HCl (900 mL, 37 ± 0.5 °C) using the paddle method at 75 rpm. Samples (5 mL) were withdrawn at 15, 30, and 45 minutes and replaced with fresh medium. Absorbance was measured at 258 nm via UV spectrophotometer ('British Pharmacopoeia, 2004).

Determination of the Maximum Absorbance and Calibration Curve for Powdered Leaves of E. camaldulensis

A 100 mg sample of *E. camaldulensis* powder was dissolved in 100 mL of 0.1N HCl. Various dilutions (1–25 mg/100 mL) were prepared and their absorbance measured at 258 nm. The calibration curve was constructed by plotting absorbance vs. concentration.

Statistical analysis

All results were expressed as mean ± standard error of the mean (SEM). Data were analyzed using one-way ANOVA. Standard deviation (SD) and relative standard deviation (RSD = SD/mean × 100%) were calculated where appropriate.

Results

All eight 300 mg Eucalyptus camaldulensis tablet formulations were prepared and optimized using the wet granulation method, and all tablets met USP and BP standards for weight, dimensions, hardness, and mechanical strength. The rapid disintegration time (0.55–2 minutes) and drug release percentage at 45 minutes (91.4–98.8%) indicated effective drug release and satisfactory tablet performance. The 2^3 factorial design identified the combined effects of critical formulation variables and established optimal conditions for robust and scalable production. The results are presented in Table 4.

The wavelength of maximum absorbance of Eucalyptus camaldulensis powdered leaf solution in 0.1 N HCl (258 nm) is shown in Figure 1.

As shown in figure 2, the maximum absorbance of the powdered leaves of Eucalyptus camaldulensis plant was found to be 258 nm.

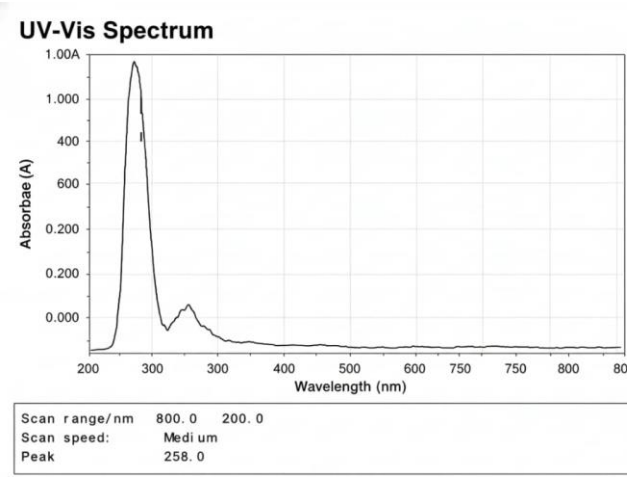

Figure 1: The wave length of maximum absorption of *E. camaldulensis* powdered leaves solution in 0.1N HCL (258nm)

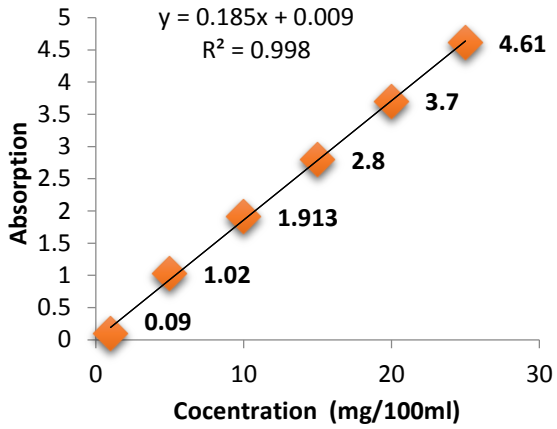

Figure 2: Calibration curve of absorption of various concentrations of *E. camaldulensis* leaves in 0.1N HCL measured at 258 nm

Table 4: Evaluation of post-compression parameters for eight different formulas of *E. camaldulensis* 300mg

Evaluation Parameters/ Formulation Code		F1	F2	F3	F4	F5	F6	F7	F8
Weight (mg)	**Mean**	303.8	306.2	309.7	309.5	305.4	309.7	309.9	306.4
	SD	2.938	2.924	3.439	1.605	3.42	1.728	1.954	2.873
	RSD%	0.967	0.95	1.1	0.51	1.11	0.55	0.62	0.93
Thickness (mm)	**Mean**	4.464	4.26	4.371	4.454	4.439	4.499	4.442	4.295
	SD	0.010	0.01	0.0113	0.0091	0.0122	0.0113	0.012	0.010
	RSD%	0.22	0.23	0.25	0.2	0.27	0.24	0.27	0.23
Diameters (mm)	**Mean**	9.084	9.077	9.08	9.079	9.094	9.134	9.119	9.099
	SD	0.0069	0.0094	0.0105	0.0128	0.0084	0.0096	0.0099	0.0099
	RSD%	0.066	0.1	0.11	0.13	0.092	0.1	0.1	0.1
Hardness (Kg)	**Mean**	4.698	4.417	5.396	4.503	4.49	5.419	5.325	4.455
	SD	0.3219	0.2805	0.2932	0.1626	0.2644	0.2456	0.2808	0.2889
	RSD%	4.698	4.417	5.396	4.503	4.49	5.419	5.325	4.455
Friability (% w/w)		0.668± 0.06	0.949± 0.08	0.753±0.05	0.991±0.02	0.923±0.04	0.791±0.07	0.673±0.10	0.868±0.06
Disintegration time (minute)		0.75±0.008	0.78±0.04	0.83±0.0	0.55±0.05	0.63±0.0	2±0.03	1.83±0.08	1.83±0.08
Percentage of drug released (%)	**15 minute**	56.01	54.03	55.02	58.96	50.122	44.22	47.17	53.30
	30 minute	88	86	85	88	82.55	76.66	79.60	82.55
	45 minute	98.8	98.4	98.5	97.29	94.84	91.40	91.40	94.84

In the evaluation of the rate of the dissolution of E. camaldulensis tablets, the regression equations obtained after fitting the trend lines to the data points, were used to calculate the amount of drug released.

The results of the dissolution test were obtained after carrying the test for 45miutes, by measuring the dissolution rate at different time intervals 15, 30 and 45 minutes. These results illustrated in a number of tables from no. 4. The concentration and percentage of active ingredient released after each time interval were estimated from the following equation of the calibration curve.

Discussion

Eight formulations (F1–F8) of Eucalyptus camaldulensis herbal antidiabetic tablets were prepared using a wet granulation method and optimized using a 2^3 full factorial design. The impact of binder concentration, disintegrant concentration and kneading time on key tablet quality parameters was evaluated. All formulations met the USP specification for weight variation, with mean weights ranging from 303.8 mg to 309.9 mg and RSD values below 1.11%. This reflects uniform die filling and proper flow properties of the granules, likely a result of efficient wet granulation (Gennaro, 1995). Tablet thickness and diameter also remained within the British Pharmacopoeia's acceptable variation limits (±5%), with thickness ranging from 4.26 mm to 4.50 mm and diameter from 9.08 mm to 9.13 mm, confirming good dimensional consistency (British Pharmacopoeia, 2002). Tablet hardness ranged between 4.42 kg and 5.42 kg, within acceptable limits for uncoated tablets. Increased binder concentration and kneading time, as observed in F3 and F6, contributed to higher hardness, likely due to stronger interparticle bonding (Ekpe et al., 2025, Rawlins, 1984; Remington's, 1980). All batches had friability values $< 1\%$, indicating sufficient mechanical strength and resistance to abrasion (USP, 2008). The disintegration time of the tablets ranged from 0.55 to 2.00 minutes, which complies with BP and USP limits (not more than 15–30 minutes) for uncoated tablets (Bi et al., 1999; USP, 2004). Formulations containing higher concentrations of disintegrant (e.g., F4) showed significantly faster disintegration, attributed to effective swelling and wicking action of croscarmellose sodium. The dissolution profiles showed that the percentages of drug released for all the 8 formulae of the Eucalyptus camaldulensis tablets which prepared by wet granulation were ranged from 44.22% to 58.96% in 15minutes, 76.60% to 88% in 30minutes and 91.40% to 98.8% in 45minutes, which were found within the British pharmacopoeia permissible limit, since the BP requires that at 45 min, not less than 70% of the prescribed or stated amount of active ingredient should have been released at completion of dissolution test (Gennaro, 1995).

The 2^3 full factorial design allowed the simultaneous assessment of three critical formulation variables and their interactions. This approach helped identify optimal conditions that balanced mechanical strength, disintegration, and dissolution performance. It also enabled precise understanding of how each factor influenced the outcome, supporting future scale-up and formulation adjustments (Mangesh et al., 2013). Standard deviation (SD) and relative standard deviation ($RSD = SD/mean \times 100\%$) were calculated to assess variability. RSD values for weight, thickness, and hardness were all under 1.2%, indicating high reproducibility and precision across formulations. This statistical consistency reinforces the robustness of the formulation and granulation process.

Conclusion

This study successfully demonstrated the feasibility of formulating E. camaldulensis into standardized herbal tablets using the wet granulation method. By applying a 2^3 full factorial design, the effects of binder concentration, disintegrant concentration, and kneading time were systematically evaluated, leading to formulations that met international pharmacopeial standards for tablet quality. All prepared formulations exhibited acceptable physical properties, rapid disintegration, and efficient drug release profiles. These findings confirm that E. camaldulensis has promising potential as an antihyperglycemic agent in solid oral dosage forms. Further pharmacological and clinical investigations are recommended to validate its efficacy and safety in human subjects and to support its integration into modern phytopharmaceutical development.

Declarations

Conflict of interest

The authors declare there is no competing interests.

Acknowledgement

A lot of thanks are given to all member staff of department of Pharmaceutics, faculty of pharmacy, National Ribat University and Medicinal and Aromatic Plants & Traditional Medicine Research Institute, National Center for Research, Sudan.

Consent for publications

The authors gave approval for the publication of the manuscript.

Funding support
This study was not funded by any organization.

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Funding acquisition: no funding
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Ethical considerations
The authors have fully adhered to ethical standards, ensuring no issues related to plagiarism, misconduct, data fabrication, falsification, duplicate publication or submission, or redundancy. The authors declare that no artificial intelligence tools were used in the preparation, writing, analysis, or editing of this manuscript. All sections of the work were entirely developed, written, and reviewed by the authors without the assistance of AI-based technologies.

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