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Formulation and Pre-Compression Characterization of *Eucalyptus camaldulensis* Herbal Tablets for Antihyperglycemic Use

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ABSTRACT

Introduction: Diabetes mellitus is a prevalent metabolic disorder that requires effective and safe treatment strategies. *Eucalyptus camaldulensis* has shown promising antihyperglycemic effects in previous studies, suggesting its potential for use in herbal drug development. However, its application in standardized oral dosage forms remains underexplored. This study aimed to formulate and characterize *E. camaldulensis* herbal tablets using wet granulation and a full 2^3 factorial design to optimize pre-compression parameters.

Methods: Powdered leaves of *E. camaldulensis* were used in eight formulations with varying concentrations of polyvinylpyrrolidone (binder), croscarmellose sodium (disintegrant), and kneading time. Granules were prepared using the wet granulation method and assessed for particle size, flow properties (bulk/tapped density, Carr's index, Hausner ratio, angle of repose), and moisture content.

Results: All formulations exhibited suitable pre-compression characteristics. Carr's index values were below 15%, Hausner ratios were below 1.25, and angles of repose were below 31°, indicating good flowability. Moisture content ranged between 1.7% and 2.7%. Mean particle sizes varied from 0.205 mm to 0.278 mm.

Conclusion: The granules demonstrated favorable flow and moisture profiles, supporting their suitability for tablet compression. These findings highlight the potential of *E. camaldulensis* for developing effective herbal antidiabetic tablets. Further studies on post-compression characteristics and clinical evaluation are warranted.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Globally, over 537 million adults are affected, and the number is expected to rise to 643 million by 2030, posing significant public health challenges, particularly in low-resource settings (International Diabetes Federation, 2021). While several synthetic oral hypoglycemic agents are available, their long-term use is often associated with side effects, high cost, and reduced patient compliance, which has led to a growing interest in herbal alternatives (American Diabetes Association, 2024; Patel et al., 2012).

Medicinal plants have gained attention as complementary therapies in diabetes management due to their multi-targeted mechanisms, affordability, and perceived safety (Modak et al., 2007). Among these, *Eucalyptus camaldulensis*, a widely distributed tree in Sudan and other tropical regions, has demonstrated promising antidiabetic, antimicrobial, and anti-inflammatory properties attributed to its rich content of polyphenols, flavonoids, and essential oils (Elhawary et al., 2014; Islam et al., 2020). In vivo studies have confirmed that *E. camaldulensis* leaf extracts significantly reduce blood glucose levels in diabetic animal models, supporting its traditional use as an antihyperglycemic agent (Abdel Moneim et al., 2018; Dawoud et al., 2015). Moreover, toxicological evaluations have indicated that the extract is safe when administered orally at therapeutic doses, with no significant adverse effects on vital organs (Bhardwaj et al., 2000; Dawoud and Shayoub, 2015).

Despite its ethnopharmacological relevance, limited studies have focused on the standardization and pharmaceutical formulation of *E. camaldulensis* into solid dosage forms. Tablets remain the most convenient and widely accepted oral drug delivery system due to their stability, accurate dosing, and patient compliance (Singh et al., 2005). However, formulating herbal tablets presents unique challenges related to flowability, compressibility, and uniformity of content, necessitating comprehensive pre-compression evaluations (Abdel Moneim et al., 2018).

Wet granulation remains a preferred technique in herbal tablet formulation as it improves the flow properties and compressibility of poorly flowing herbal powders (Eidi et al., 2009). Employing factorial design as a statistical tool allows optimization of formulation variables such as binder concentration, disintegrant levels, and kneading time, enhancing formulation robustness and reducing development time (Ojo et al., 2014; Orisakwe et al., 2003).

Therefore, the objective of this study is to design, formulate, and evaluate Eucalyptus camaldulensis tablets using wet granulation and a 2^3 full factorial design to optimize key formulation parameters. This research aims to develop a scientifically validated, pharmaceutically acceptable, and safe herbal antidiabetic tablet that can serve as a potential alternative in diabetes management.

Materials and Methods

The leaves of *Eucalyptus camaldulensis* were collected in August 2022 from the Forest Research Center, Sudan. Botanical identification and authentication were carried out by Prof. Mohammed El-Mokhtar and Prof. Dawoud H. Dawoud from the Agricultural Research Corporation, Ministry of Agriculture and Irrigation. The leaves were cleaned to remove foreign matter, shade-dried, and ground into a fine powder using a laboratory mill.

Formulation design using 2^3 full factorial design

A full 2^3 factorial experimental design was employed to investigate the effect of three formulation variables—binder concentration (polyvinylpyrrolidon PVP), disintegrant concentration (croscarmellose sodium), and kneading time—on the pre-compression properties of *E. camaldulensis* granules (Table 1). Eight experimental formulations were developed according to the factorial combinations (Heywood, 1948) (Tables 2 and 3).

The design was analyzed using Design-Expert software (Stat-Ease Inc., Minneapolis, USA), and statistical significance was assessed via ANOVA.

The dependent variables evaluated included angle of repose, Carr's index, Hausner ratio, moisture content, and particle size. Each experiment was conducted in triplicate, and data were reported as mean ± standard deviation.

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)
Factor 1- (X1)	Amount of binder	2% (W /W)	4% (W /W)
Factor 2-(X2)	Amountof disintegrant- croscarmellose sodium	2% (W /W)	4% (W /W)
Factor 3- (X3)	Kneading time	6 Minutes	12 minutes

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

Run	Formula	Coded values			Actual values		
		X1	X2	X3	X1 Binder Conconcentration (%)	X2 Disintigrant Conconcentration (%)	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

Table 3: Percentage composition of *Eucalyptus* camaldulensis 300 mg tablets

Batch Code	Ingredients (%/tablet)						
	Polyvinyl pyrrolidon	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

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

Preparation of Granules

Wet Granulation Method

The dried *E. camaldulensis* leaf powder was passed through a 60-mesh sieve to ensure uniform particle size. Each formulation was prepared using the wet granulation method. The required amounts of polyvinylpyrrolidone (PVP, used as a binder) were dissolved in purified water and added gradually to the powder blend containing *E. camaldulensis* powder and croscarmellose sodium (used as a disintegrant).

Kneading was performed manually for the assigned time according to each factorial run. The resulting wet mass was passed through a 2 mm sieve to obtain granules, which were then dried in a hot air oven at 40°C for 1 hour. A laboratory blender was used for homogenization.

The quantity of water added (30 ml per 50 g of powder) was optimized through preliminary trials to achieve the desired granule consistency without overwetting or underwetting.

Evaluation of pre-compression parameters

Particle size analysis

The particle size distribution of the granules was determined using an automatic sieve shaker. A stack of standard sieves with mesh sizes of 850 µm, 600 µm, 425 µm, 250 µm, 180 µm, 150 µm, and 63 µm was arranged in descending order, with the largest mesh (850 µm) at the top and the smallest (63 µm) at the bottom. Approximately 30 g of granules were placed into the top sieve, and the assembly was covered and subjected to vibration for 10 minutes.

After sieving, the granules retained on each sieve were carefully collected and weighed. The percentage weight of granules retained on each sieve was calculated to determine the particle size distribution (Mangesh et al., 2013).

The mean particle size was then calculated according to the method described in the British Pharmacopoeia (2007), using the following equation:

The mean particle size = Σ [(% retained) x (mean aperture)] /100

Evaluation of flow properties of granules

Bulk density (BD)

Bulk density was determined by pouring gently 30 gm of sample through a glass funnel into 100 ml graduated cylinder. The volume occupied by the sample was recorded (Ansel et al., 2005).

Bulk density was calculated using formula:

BD= Mass of powder/Untapped volume

Tapped density (TD)

Tapped density was measured using a graduated cylinder. An accurately weighed quantity of the

granule sample was carefully transferred into the cylinder with the help of a funnel. The initial (untapped) volume was recorded. The cylinder was then subjected to repeated tapping on a horizontal surface until no further reduction in volume was observed (Avula and Veesam, 2013).
The final tapped volume was recorded, and the tapped density was calculated using the following formula:
TD = Mass of powder/Tapped volume

Hausner ratio
The Hausner ratio was determined by using fallowing equation according to wells, 2002 (Wells, 2002).
Hausner Ratio = TD/BD

Carr's Index
The Carr's Index was determined by fallowing equation according to wells, 2002 (Wells, 2002).
Carr's Index = [(T D - BD) / T D] × 100

Determination of Angle of Repose
The flow properties of the granules were evaluated by determining the angle of repose. A sample of 10 g of each formulation was gently poured into an open-ended glass cylinder (2.8 cm diameter) positioned vertically on a flat surface. Upon lifting the cylinder, the granules flowed freely to form a conical heap (Vaja et al., 2010).
The height (h) of the resulting cone and the radius (r) of its base were measured, and the angle of repose (θ) was calculated using the following equation:
Angle of Repose (θ) = $\tan^{-1}(h / r)$
where h = height of the powder pile,
r = radius of the base.

Determination of Moisture Content
The moisture content of the granules was determined using an infrared moisture analyzer (KERN LP 16, Germany), which incorporates a precision balance to detect weight loss during drying. Infrared radiation in the wavelength range of 2–3.5 μm was applied from below the sample to facilitate heating and moisture evaporation.
This technique offers the advantage of rapid analysis and is suitable for substances that may degrade at higher temperatures used in conventional ovens. Approximately 1 g of granules was analyzed, and the moisture content was calculated automatically by the instrument as a percentage of the initial sample weight (Hussien, 2012).

Results
Particle size analysis
The mean particle sizes of formulations F1 to F8 were determined to be 0.266 mm, 0.205 mm, 0.240 mm, 0.255 mm, 0.278 mm, 0.224 mm, 0.242 mm, and 0.277 mm, respectively. These results indicate that the particle size of all batches fell within the acceptable pharmaceutical range, supporting their suitability for compression into tablets.

Flow Properties of Granules
Table 4 presents the values for bulk density, tapped density, Carr's Index, Hausner ratio, and angle of repose for all formulations. The Carr's Index values ranged from 1.38% to 14.0%, with the lowest observed in F1 (1.38%) and the highest in F6 (14.0%). Hausner ratios ranged from 0.99 to 1.13, and angles of repose ranged from 25° to 30°. All values suggest good to excellent flowability for the granules.

Moisture Content (Loss on Drying)
The moisture content of the granules (Table 5) ranged between 1.7% (F1) and 2.7% (F8). All formulations were within acceptable limits, confirming adequate drying and low moisture retention.

Table (4): Evaluation of pre-compression parameters for granules of different formula of tablets.

Formula No.	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner ratio	Angle of repose
F1	0.426±0.04	0.432±0.03	1.38±1.9	0.99±0.02	25^0±0.66
F2	0.413±0.01	0.442±0.01	6.56±1.2	1.07±0.01	27^0±0.61
F3	0.435±0.07	0.462±0.02	5.84±1.1	1.06±0.05	26^0±0.52
F4	0.499±0.02	0.531±0.01	6.02±1.3	1.06±0.04	25^0±0.44
F5	0.321±0.001	0.352±0.01	8.8±1.7	1.09±0.01	28^0±0.21
F6	0.424 ±0.032	0.430 ±0.3	14.0 ±1.03	1.014±0.02	30^0±0.32
F7	0.376±0.02	0.427 ±0.03	11.857±0.31	1.130±0.01	30^0±0.61
F8	0.401±0.05	0.443±0.01	9.48±1.5	1.10±0.01	29^0±0.72

All values are expressed a mean ±SD, n=3.

Tablet 5: Results of loss on drying for granules of the eight different formulae.

Formula code	F1	F2	F3	F4	F5	F6	F7	F8
LOD (%)	1.7±0.50	2.4±0.31	1.9±0.14	2.4±0.23	2.5±0.42	2.6±0.11	2.6±0.09	2.7±0.1

All values are expressed a mean ±SD, n=3.

Discussion

The particle size distribution observed in this study aligns with established findings that uniform particle size promotes consistent flow and compressibility. Larger particles generally support better flow, though they may reduce tablet strength due to lower surface area for bonding. An optimal balance, as seen in these results, is necessary for high-quality tablets.

The excellent flow properties of F1 can be attributed to its low Carr's Index (1.38%), low Hausner ratio (0.99), and narrow angle of repose (25°), which reflect minimal interparticle friction and cohesive forces. This suggests that F1 may have benefited from an ideal combination of binder concentration and kneading time.

In contrast, the higher Carr's Index values in F6 (14.0%), F7 (11.86%), and F8 (9.48%) indicate comparatively poorer flow. These may result from suboptimal binder or disintegrant concentrations, or over-kneading, leading to agglomeration and inconsistent granule morphology.

Statistical analysis (ANOVA) showed that binder concentration significantly influenced Carr's Index and angle of repose ($p < 0.05$), whereas kneading time did not significantly affect bulk density or Hausner ratio ($p > 0.05$). These findings are consistent with literature highlighting the critical role of binder in determining powder behavior.

Uniform moisture content (1.7% to 2.7%) across formulations demonstrates effective drying and stable granule structure, which is vital for further processing and storage. No outliers in particle size suggest consistency in granulation and sieving procedures.

Overall, F1 emerged as the optimal formulation with superior pre-compression characteristics. It is the most promising candidate for proceeding to compression and post-compression evaluations.

Conclusion

The present study successfully formulated and evaluated *E. camaldulensis* herbal tablets using a full 2^3 factorial design. Pre-compression characterization demonstrated acceptable flow and density properties across all formulations, with F1 emerging as the most promising candidate due to its superior granule flowability, compressibility, and uniform particle size.

These results support the feasibility of developing a standardized antidiabetic herbal tablet from *E. camaldulensis*. Further research is warranted to assess post-compression parameters, in vitro drug release, and clinical efficacy in diabetic patients.

Declarations

Conflict of interest

The authors declare there is no competing interests.

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Consent for publications

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Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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