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Original article

Granulation of Paracetamol Using Honey as a Natural Binder: A Comparative Study with Polyvinylpyrrolidone

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Abstract
Granulation is a fundamental pharmaceutical process that enhances the flowability, compressibility, and uniformity of powders used in solid dosage forms. This study investigates the feasibility of using honey as a natural binder in the wet granulation of paracetamol and compares its performance with polyvinylpyrrolidone (PVP K30), a conventional synthetic binder. Five formulations containing 5% paracetamol, 82.5% lactose, and 12.5% binder (either PVP or honey) were prepared using wet granulation. The resulting granules were evaluated for particle size distribution, percentage yield, flow properties (angle of repose, Hausner ratio, and Carr's index), and friability. PVP-based granules demonstrated superior performance with higher yields (94-98.76%), lower angles of repose (24-26°), and consistently lower friability (2.16-3.21%) compared to honey-based granules, which showed yields of 88-89.82%, angles of repose of 28-30°, and more variable friability (2.50-13.2%). Both binders exhibited excellent flowability based on the Hausner ratio (1.04-1.13) and Carr's index (<12%). While PVP remains the more reliable binder for industrial applications, honey demonstrated adequate binding capacity and acceptable flow properties, suggesting its potential as a natural, biodegradable, and cost-effective alternative. However, standardization and optimization are required to address honey's inherent variability and hygroscopicity before it can be considered a full replacement in conventional pharmaceutical manufacturing.
Keywords. Granulation, Honey, Natural Binder, Paracetamol, Polyvinylpyrrolidone, Wet Granulation.

Introduction

Pharmaceutical granulation is a critical process in solid dosage form manufacturing whereby dry primary powder particles are agglomerated to form larger, multi-particle entities known as granules [1]. The primary purpose of this size enlargement process is to improve the flow properties and compressibility of the powder mixture, prevent segregation of components, and control the rate of drug release. It is an essential step in the production of tablets and capsules, ensuring consistent weight, uniform drug content, and desired drug release characteristics [2]. The necessity of granulation arises from the need to overcome technological challenges posed by raw powder materials. Fine, cohesive powders, particularly active pharmaceutical ingredients (APIs), exhibit poor flow properties due to high inter-particulate friction and cohesive forces, leading to inconsistent fill volume and tablet weight variation. Wet granulation is the most widely used technique, involving the addition of a granulating liquid or binder solution to facilitate particle agglomeration [3].

The binder plays a critical role in imparting cohesiveness to the powder mass, ensuring adequate mechanical strength in the final dosage form. Synthetic binders such as polyvinylpyrrolidone (PVP) are commonly used due to their consistent performance, strong binding properties, and reproducibility [2]. However, growing interest in natural, biodegradable, and non-toxic alternatives has prompted investigation into natural binders such as starch, gelatin, gum arabic, and honey. Honey, a natural substance produced by bees, has a hygroscopic nature and adhesive properties that make it attractive for pharmaceutical applications as a granulation binder. Its composition includes sugars (primarily fructose and glucose), water, organic acids, enzymes, and bioactive compounds with antimicrobial and antioxidant activities [4]. However, its natural variability, susceptibility to microbial degradation, and inferior moisture resistance present challenges that require investigation [5].

Honey's known antimicrobial, antioxidant, and wound-healing properties could provide additional therapeutic benefits in certain formulations [4,5]. This study aims to evaluate the performance of honey as a natural binder in the wet granulation of paracetamol and compare it with the conventional synthetic binder PVP K30. The evaluation focuses on granule yield, flow properties (angle of repose, Hausner ratio, Carr's index), and friability. The findings will contribute to understanding the potential of honey as a sustainable, biocompatible alternative in pharmaceutical granulation.

Materials and Methods

Materials

Paracetamol (active pharmaceutical ingredient) was obtained from a local supplier. Lactose monohydrate 200M was purchased from Dmv (Veghel, The Netherlands). Polyvinylpyrrolidone (PVP Kollidon K30) was purchased from BASF (Ludwigshafen, Germany). Honey was purchased from the local market. Distilled water was used as the granulating liquid.

Preparation of Wet Granules

Five formulations were prepared for each binder (PVP or honey), each containing 5% paracetamol, 82.5% lactose, and 12.5% binder (Table 1). The total batch weight was maintained at 100 g for each formulation.

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Table 1. Formulation Composition for Paracetamol Granules

Ingredient	Formulation (PVP as binder)	Formulation (Honey as binder)
Paracetamol	5%	5%
Lactose	82.5%	82.5%
PVP	12.5%	none
Honey	none	12.5%

Note: Distilled water was used as the granulating solvent for both binders

Preparation Procedure

For PVP-based granules, the required ingredients were weighed accurately. Paracetamol and lactose were mixed thoroughly. PVP was dissolved in a calculated amount of distilled water to form a binder solution. The binder solution was added gradually to the powder mixture while kneading manually until a wet mass was formed. The wet mass was passed through an oscillating granulator (mesh size 1.25 mm) to obtain wet granules. The wet granules were weighed to determine percentage loss, then dried in an oven at a temperature not exceeding 40°C until constant weight was achieved [3]. For honey-based granules, the procedure was modified to accommodate the viscosity of honey. The calculated amount of honey was mixed with distilled water until a homogeneous dispersion was achieved. This mixture was then added to the powder blend of paracetamol and lactose, followed by kneading to form a wet mass. The wet mass was granulated using an oscillating granulator and dried under identical conditions. Dried granules were passed through a vibratory sieve shaker for 15 minutes using sieves of 250 µm and 750 µm. Granules smaller than 250 µm and larger than 750 µm were excluded, and the retained fraction (250-750 µm) was collected for evaluation.

Evaluation of Granules

The produced granules are evaluated as described by Aulton [1]. The methods of calculation are mentioned in our previously published work [6]. The formulation of each binder was repeated five times (F1 to F5) to examine the result's reproducibility. Results were expressed as mean ± standard deviation (SD). The evaluation results of the produced granules are represented in the following tables.

Results

Granule Yield

The percentage yield of granules prepared with PVP or honey is presented in (Table 2 and Figure 1). PVP-based granules consistently produced higher yields ranging from 94% to 98.76%, with a mean yield of 97.14%. Honey-based granules showed lower yields ranging from 88% to 89.82%, with a mean yield of 88.74%.

Table 2. Percentage Yield of Granules Prepared with PVP or Honey as Binder

Formulation	PVP Yield (%)	Honey Yield (%)
F1	98.76	88.74
F2	97.61	88.03
F3	94.00	89.82
F4	98.10	88.00
F5	97.22	89.12
Mean ± SD	97.14 ± 1.89	88.74 ± 0.75

Flow Properties

Angle of Repose

The angle of repose values for PVP and honey granules are presented in (Table 3). PVP granules exhibited lower angles of repose (24.12° to 26.56°), indicating better flowability, while honey granules showed higher angles (28.77° to 30.53°). Both binders produced granules with angles of repose within the acceptable range (<35°).

Table 3. Angle of Repose of Granules Prepared with PVP or Honey

Formulation	(PVP) Angle of Repose (°)	(Honey) Angle of Repose (°)
F1	26.56	29.66
F2	25.20	30.53
F3	24.12	29.38
F4	24.90	28.77
F5	25.63	29.12
Mean ± SD	25.28 ± 0.97	29.49 ± 0.65

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Hausner Ratio

The Hausner ratio values are presented in (Table 4). Both binders exhibited similar average Hausner ratios (1.07 for both), indicating excellent flow properties. PVP showed greater variability (range: 1.04-1.13) compared to honey (range: 1.06-1.10).

Table 4. Hausner Ratio of Granules Prepared with PVP or Honey as binder

Formulation	(PVP) Hausner Ratio	(Honey) Hausner Ratio
F1	1.08	1.08
F2	1.04	1.06
F3	1.13	1.10
F4	1.04	1.06
F5	1.06	1.07
Mean ± SD	1.07 ± 0.03	1.07 ± 0.01

Carr*'s Index*

The Carr's index values are presented in (Table 5). Both binders showed excellent compressibility with Carr's index values below 12%. PVP exhibited a wider range (3.84% to 11.76%) compared to honey (5.66% to 9.62%), indicating greater variability in PVP performance.

Table 5. Carr's Index of Granules Prepared with PVP or Honey as binder

Formulation	(PVP) Carr's Index (%)	(Honey) (%) Carr's Index
F1	7.54	7.54
F2	3.84	5.88
F3	11.76	9.62
F4	3.84	5.66
F5	5.76	5.98
Mean ± SD	6.55 ± 3.36	6.94 ± 1.45

Friability

The friability test results are presented in (Table 6). PVP granules demonstrated low and consistent friability values (2.16% to 3.21%), indicating strong, durable granules. Honey granules showed highly variable results (2.50% to 13.2%), with some formulations exhibiting poor granule strength and mechanical resistance.

Table 6. Friability of Granules Prepared with PVP or Honey

Formulation	(PVP) Friability (%)	(Honey) (%) Friability
F1	2.16	3.03
F2	2.56	10.16
F3	3.15	13.20
F4	2.31	2.66
F5	3.21	2.50
Mean ± SD	2.68 ± 0.46	6.31 ± 5.01

Discussion

This comparative study evaluated the performance of honey as a natural binder against PVP K30 in the wet granulation of paracetamol. The results demonstrate clear differences in binding efficiency, mechanical strength, and processing consistency between the two binders, which are discussed below in terms of granule yield, flow properties, and mechanical integrity. PVP formulations consistently produced higher yields (94-98.76%) compared to honey formulations (88-89.82%). Although both binders met the acceptable pharmaceutical yield range (85-102%), the difference of approximately 5-10% indicates superior process efficiency with PVP [7]. This superior yield may be attributed to several factors: first, PVP's strong film-forming and adhesive properties promote the formation of stable solid bridges during drying [8]; second, PVP solutions have lower viscosity compared to honey, allowing more uniform distribution and better wetting of powder particles; third, honey's hygroscopic nature may cause reabsorption of moisture during processing, leading to increased adhesion to equipment surfaces and material losses. The lower yield of honey-based granules suggests increased fines formation and reduced granule integrity during processing. Honey's complex composition, containing sugars, organic acids, and enzymes, may contribute to batch-to-batch variability in binding efficiency [9]. Additionally, the viscous nature of honey may lead to the formation of larger, more cohesive agglomerates that are more susceptible to breakage during drying and sieving operations [10]. These findings align with literature indicating that

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synthetic binders such as PVP provide more predictable and reproducible granulation performance compared to natural binders, whose variability can significantly influence process outcomes [11,12].

The flow properties of granules are critical for ensuring consistent die filling during tablet compression and capsule filling operations [3,13]. In this study, both binders produced granules with acceptable flow characteristics based on all evaluated parameters. Angle of Repose: PVP granules showed lower angles of repose (24-26°), indicating better flowability compared to honey granules (28-30°). While both formulations fall within the acceptable "good to passable" flow range (<35°), PVP demonstrates superior flow characteristics. The consistently higher angle of repose observed with honey may be explained by increased cohesiveness due to residual moisture content, the sticky nature of sugars (fructose and glucose) present in honey, and potentially irregular granule surface morphology [14]. Hausner Ratio and Carr's Index: Both binders exhibited excellent flowability based on Hausner ratio (≈1.04-1.13) and Carr's index (<12%). However, interesting differences emerged: PVP showed greater variability in Carr's index (3.84-11.76%), while honey displayed more consistent compressibility values (5.66-9.62%). This suggests that honey may provide more uniform compaction properties, potentially due to its plasticizing effect during compression. These findings indicate that honey can provide acceptable flow performance when properly processed, supporting the work of other researchers who have explored natural binders in granulation [15]. The most significant difference between the two binders was observed in granule friability. PVP granules demonstrated consistently low friability (2.16-3.21%), indicating strong, durable granules capable of withstanding mechanical stresses during processing, handling, and transportation [16]. This mechanical strength is attributed to PVP's excellent film-forming properties and the formation of strong solid bridges between particles during drying [17,18]. In contrast, honey granules showed highly variable friability (2.50-13.2%), with two formulations (F2 and F3) exhibiting exceptionally high friability (>10%). This variability highlights the challenges associated with using natural binders, particularly honey, in pharmaceutical granulation. The high friability in some formulations suggests poor inter-particulate bonding, possibly due to:

1. Non-uniform distribution: Honey's high viscosity may hinder uniform distribution throughout the powder mass, leading to regions with insufficient binding.
2. Variability in honey composition: Natural honey varies in sugar composition, moisture content, and enzyme activity depending on floral source and processing, affecting its binding performance.
3. Hygroscopicity: Honey's tendency to absorb moisture may lead to plasticization of the solid bridges, reducing granule strength [19].

Despite these challenges, some honey formulations (F4 and F5) demonstrated friability values (2.50-2.66%) comparable to PVP, indicating that with proper optimization, honey can produce mechanically robust granules. This suggests that factors such as batch-to-batch variability, processing conditions, and honey concentration significantly influence performance.

Conclusion

This comparative study evaluated the performance of honey as a natural binder against polyvinylpyrrolidone (PVP K30) in the wet granulation of paracetamol. The results demonstrate clear differences in binding efficiency, mechanical strength, and processing consistency between the two binders. While polyvinylpyrrolidone remains the more reliable and industrially preferred binder for wet granulation of paracetamol, honey shows potential as a natural binder for certain applications. With further optimization and standardization, honey could contribute to more sustainable and biocompatible pharmaceutical manufacturing, particularly in formulations where its additional bioactive properties provide therapeutic benefits. Despite its limitations, honey offers compelling advantages as a natural binder. Its natural origin, biodegradability, and non-toxicity align with growing demand for environmentally sustainable and patient-friendly formulations. Furthermore, honey is readily available and potentially more cost-effective than synthetic binders.

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Conflict of interests

The authors declare no conflicts of interest.

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