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Original article

Evaluation of Honey as a Natural Binder in Pharmaceutical Granulation: A Comparative Study with Polyvinylpyrrolidone

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A B S T R A C T

This study investigates the potential of honey, a natural and biocompatible material, as an alternative binder in wet granulation that can be particularly suitable for herbal and pediatric formulations. Lactose monohydrate was used as the model filler. Granules were prepared using wet granulation with distilled water as the granulating fluid. Five concentrations of synthetic binder PVP (1.5–3.5% w/w) and five concentrations of honey (1.5–3.5% w/w) were initially evaluated. Based on initial yield results, a subsequent optimization phase was conducted with honey concentrations ranging from 1.5% to 13.5% w/w at a fixed, lower water concentration (5.5% w/w). The properties of the resulting granules were investigated. The optimal honey formulation was then subjected to a reproducibility study over five batches. The initial results of this study were optimized by increasing honey concentration to 12.5% (with 5.5% water), which significantly improved the yield to 88.3%. This formulation exhibited excellent flow properties (angle of repose: 32.03°, Hausner ratio: 1.07, Carr's index: 6.83%) and low friability (9.4%), comparable to high-concentration PVP granules. The reproducibility study confirmed the consistency of the 12.5% honey formulation, with minimal batch-to-batch variability. Therefore, in comparison to PVP, honey can be considered an effective and sustainable natural binder for pharmaceutical granulation because at a concentration of 12.5%, it produces granules with excellent yield, flowability, and mechanical strength.

Introduction

Granulation is a fundamental unit operation in the pharmaceutical industry, primarily used to convert fine powder particles into larger, free-flowing, and durable granules. This process is essential for ensuring uniformity in Tablet weight and drug content, improving compressibility, and preventing segregation of the blend. In pharmaceutical applications, granules typically range in size from 0.2 to 4.0 mm, depending on their intended use [1].

Wet granulation is the most widely employed method, where a granulating fluid, often containing a binder, is added to a powder bed to form agglomerates. Binders are critical excipients that promote particle adhesion and provide the necessary strength to granules. Traditionally, natural polymers like starch and gelatin were used, but they have been largely replaced by synthetic alternatives such as polyvinylpyrrolidone (PVP) and cellulose derivatives [2]. While effective, these synthetic binders are associated with high costs, non-renewable sourcing, and potential concerns for certain patient demographics seeking natural products. There is a growing interest in the pharmaceutical sciences to explore natural, sustainable, and biocompatible excipients [3].

Honey, a complex natural substance produced by bees, is composed primarily of sugars (fructose and glucose), along with water, enzymes, and various phytochemicals [4]. It is widely recognized for its nutritional value, humectant properties, and ability to form bridges between particles. These characteristics make it a promising candidate as a natural binder honey as a natural binder in wet granulation, in comparison with the widely used synthetic binder, PVP [5]. Evaluation of the produced granules included the yield, particle size distribution, flow properties (angle of repose, Hausner ratio, Carr's index), and friability [6]. The study also seeks to identify the optimal concentration of honey for achieving high-quality granules and to validate the reproducibility of the process.

Materials and Methods

Materials

α-Lactose monohydrate 200M (DMV, Veghel, The Netherlands) – used as the primary filler. Polyvinylpyrrolidone (PVP, Kollidon® K30) (BASF, Ludwigshafen, Germany) – used as the synthetic binder (control). Natural honey (purchased from a local Libyan market) – used as the natural binder. Distilled water – used as the granulating fluid.

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Granule Preparation

Granules were prepared by wet granulation. For each formulation, lactose (100 g basis) was placed in a stainless-steel bowl. The binder (PVP or honey) was either dry-mixed with lactose (for PVP) or pre-dissolved/mixed with water (for honey). The granulating liquid (water or binder solution) was added gradually while kneading by hand until a wet mass was formed. The wet mass was passed through an oscillating granulator (sieve size 2.0 mm) to form wet granules. The granules were dried in a tray dryer at 40°C until a constant weight was achieved.

Three sets of formulations were prepared:

1- Water-only formulations (F1-F5): To determine the optimal water concentration, granules were prepared with 100% lactose and different concentrations of water, as shown in (Table 1).

Table 1. The formulations of 5 different water concentrations.

Ingredients	F1	F2	F3	F4	F5
Lactose	100%	100%	100%	100%	100%
Water	5.5%	6.5%	7.5%	8.5%	9.5%

2- PVP formulations (F6-F10): Granules were prepared with different concentrations of PVP and a fixed water concentration of 8.5% (the best from the water-only series), as shown in (Table 2).

Table 2. The formulations of 5 different PVP concentrations.

Ingredients	F6	F7	F8	F9	F10
Lactose	98.5%	98%	97.5%	97%	96.5%
PVP	1.5%	2%	2.5%	3%	3.5%
Water	8.5%	8.5%	8.5%	8.5%	8.5%

3- Honey formulations (F11-F15): Granules were prepared with different honey concentrations and a fixed water concentration of 8.5%, as shown in (Table 3).

Table 3. The formulations of 5 different honey concentrations.

Ingredients	F11	F12	F13	F14	F15
Lactose	98.5%	98%	97.5%	97%	96.5%
Honey	1.5%	2%	2.5%	3%	3.5%
Water	8.5%	8.5%	8.5%	8.5%	8.5%

Evaluation of Granules

All dried granules were sieved using a vibratory sieve shaker for 15 minutes. The fraction between 250 µm and 750 µm was collected for further testing.

Granules Yield

The granulation yield was calculated as the percentage of dried granules retained within the 250-750 µm size range relative to the total weight of dried granules. The granule yield was calculated as described by Aulton [7].

Particle Size Separation

Particle size separation was performed by sieving according to the European Pharmacopoeia (Ph. Eur.) guidelines [6]. A set of sieves ranging from 250–1000 µm was arranged in descending order, with a collection pan at the bottom. Before use, sieves were cleaned, dried, and weighed to establish a baseline. Granule samples were placed on the top sieve, and the stack was mounted on a sieve vibrator operated for 10–15 minutes at a controlled amplitude. After sieving, each fraction was weighed to determine particle size distribution. The results were compared against pharmacopeial specifications or product monographs to confirm compliance. As noted in Ph. Eur., acceptance criteria for granule size distribution vary depending on the formulation and intended use [6].

Flow Properties

Angle of Repose (θ): Measured using the fixed funnel method. A glass funnel with a 5 mm orifice was fixed 2 cm above a flat surface. The granules were allowed to flow through the funnel to form a cone. The height (h) and radius (r) of the cone were measured, and the angle of repose was calculated as $\tan \theta = h/r$ [7].

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Bulk Density (BD) and Tapped Density (TD)
A 50 g sample of granules (250-750 µm) was placed in a 100 mL graduated cylinder. The bulk volume (V0) was recorded. The cylinder was then tapped 1500 times using a tapping machine (J. Englesman, Ludwigshafen, Germany), and the tapped volume (Vf) was recorded. BD and TD were calculated as described by Aulton [7]. *Hausner Ratio* and *Carr's Index* were calculated using the formulas:
Hausner Ratio = TD / BD
[7] *Carr's Index* (%) = [(TD - BD) / TD] × 10

Friability
Granule friability was determined using a friabilator (PTF E Pharma Test, Hainburg, Germany). A 10 g sample of granules (250-750 µm) was placed in the drum with 200 glass beads. The drum was rotated at 25 rpm for 10 minutes. After the test, the glass beads were removed by sieving, and the weight of granules retained on a 250 µm sieve (W2) was recorded. Friability was calculated as mentioned by Aulton [7]. All evaluations were performed in triplicate, and results were expressed as mean ± standard deviation (SD).

The Optimization of Honey Formulation
Following the initial evaluation, an optimization phase was conducted. The water concentration was reduced to 5.5% to improve yield, and the honey concentration was increased in a stepwise manner (1.5%, 3.5%, 5%, 8%, 10%, 11.5%, 12.5%, 13.5% w/w), the formulation code as F16 to F23, respectively, and the evaluation of the produced granule.

Results

Particle size analysis
As it appears in Table 4, the granules prepared with honey as a binder (F11–F15) consistently showed the largest mean particle sizes, ranging from 465.1 µm to 471.4 µm with an average of about 469.5 µm. The variation among these samples was minimal, with a narrow range of 6.3 µm and a standard deviation of only 2.6 µm. This high level of uniformity highlights the effectiveness of honey, even at lower concentrations, in producing granules of stable and consistent size. In comparison, granules prepared with PVP as a binder (F6–F10) demonstrated intermediate particle sizes, ranging from 410 µm to 440 µm, with an average of approximately 426.7 µm. Granules prepared with water alone (F1–F5) exhibited the smallest particle sizes, with values ranging from 242.5 µm to 428.9 µm and an average of about 380.9 µm.

Table 4. Mean Particle Diameter (MPD) of granules under different binder conditions

Formula	MPD (µm)	Binder Condition
F1	428.9	Water only
F2	411.6	Water only
F3	412.3	Water only
F4	242.5	Water only
F5	409.5	Water only
F6	415.0	PVP binder
F7	410.0	PVP binder
F8	440.0	PVP binder
F9	435.3	PVP binder
F10	433.0	PVP binder
F11	465.1	Honey binder
F12	471.4	Honey binder
F13	468.8	Honey binder
F14	471.3	Honey binder
F15	470.8	Honey binder

Granules Yield
As shown in (Table 5) water-only granules (F1-F5) have poor yield (35-41.5%) and high friability (35-57.5%), confirming the necessity of a binder.

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Table 5. Evaluation of flow properties, friability, and yields of the granules without a binder, but only water. (Results expressed as Mean ± SD, n=3).

Formula code	Bulk density	Tapped density	Hausner ratio	Carr's index%	Angle of repose	Friability%	%yield
F1	0.48±1.08	0.54±1.26	1.12±1.01	11±1.64	32.1±0.21	57.5±1.66	35%
F2	0.44±0.17	0.47±1.05	1.08±0.10	7.8±0.41	31.2±0.00	53.1±1.27	36%
F3	0.44±1.03	0.50±1.98	1.13±0.51	12±1.11	31.8±0.32	40.2±0.96	37.3%
F4	0.43±1.85	0.48±0.11	1.11±0.38	10±1.30	31.6±0.14	35.4±1.35	39.7%
F5	0.43±0.68	0.49±0.21	1.13±1.41	11.6±1.01	31.1±0.24	42.9±1.79	41.5%

However, PVP-bound granules (F6-F10) showed a concentration-dependent improvement in the yield. The best results were at 3.5% PVP, which showed a high yield (74%), low friability (4.3%), and good to excellent flowability (Carr's Index: 8.43%, Angle of Repose: 29.0°) as it's summarized in (Table 6).

Table 6. Evaluation of flow properties, friability, and yields of granules prepared by PVP as a binder (Results expressed as Mean ± SD, n=3).

Formula code	Bulk density	Tapped density	Hausner ratio	Caar' index	Angle of repose	Friability (%)	Yield (%)
F6	0.36±0.01	0.43±1.22	1.19±1.54	15.01±0.23	32.1±0.25	20.1±025	48.4
F7	0.38±2.14	0.47±2.01	1.15±0.47	15.01±0.47	32.2±2.44	17.8±1.32	50
F8	0.45±1.27	0.48±1.34	1.06±1.65	9.89±0.66	31.4±0.99	12.3±0.91	53
F9	0.44±0.62	0.47±0.15	1.05±0.18	9.05±0.69	29.2±1.09	8.4±8.4	72
F10	0.43±0.08	0.46±1.07	1.04±0.25	8.43±0.01	29±0.44	4.3±4.3	74

Honey-bound granules (F11-F15) at the same water level showed moderate performance, with a 3.5% concentration yielding 57% and a Carr's Index of 9.74%. While promising, the yields for honey were suboptimal, prompting further optimization as seen in (Table 7).

Formula code	Bulk density	Tapped density	Hausner ratio	Carr's index	Angle of repose	Friability (%)	Yield (%)
F11	0.39±0.12	0.47±1.02	1.21±0.11	16.9±1.01	32.5±0.46	26.5±0.15	42.06
F12	0.46±0.18	0.51±1.51	1.10±2.64	15.8±1.11	32.1±0.36	26.2±1.7	45
F13	0.45±1.28	0.46±1.32	1.08±0.47	12.4±0.29	32.1±0.35	26.1±0.42	48
F14	0.43±1.6	0.49±0.7	1.16±0.91	12.2±1.98	32.1±0.41	24.7±1.9	53
F15	0.40±0.26	0.43±0.20	1.07±0.56	9.74±2.1	29.9±1.58	23.8±0.61	57

Table 7. Evaluation of flow properties, friability, and yields of granules prepared by honey as a binder (Mean ±SD, n=3).

Optimization of the honey-bound granulation formula

Because the yield of the granulation process using honey as a binder was not sufficiently high, we examined the effect of reducing the water concentration in the formula to 5.5% (the lowest feasible level) and gradually increasing the honey concentration to optimize the granulation formula and improve the yield. The ingredient concentrations of each proposed formula are given in (Table 8).

Table 8. The concentration of the ingredients in the optimized formulations

Ingredients	F16	F17	F18	F19	F20	F21	F22	F23
lactose	98.5%	96.5%	95.0%	92.0%	90%	88.5%	87.5%	86.5%
honey	1.5%	3.5%	5.0%	8.0%	10.0%	11.5%	12.5%	13.5%
water	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%

We also evaluated the properties of the granules produced from each formula prepared for the purpose of optimizing the honey-bound granulation. The results are presented in (Table 9).

Table 9. Evaluation of the granules produced by the optimized formulations

Formula code	Honey %	Hausner ratio	Carr's index %	Angle of repose	Friability%	Yield%
F16	1.5%	1.13±0.02	12.2±1.60	32.8±0.50	38.4±0.37	30
F17	3.5%	1.18±0.30	9.29±0.19	32.8±0.55	38±1.09	53.3
F18	5%	1.16±0.51	13.9±0.50	32.6±0.14	31±1.20	60
F19	8%	1.09±0.11	9.03±1.11	32.6±0.67	29.9±0.88	75.3

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F20	10%	1.08±0.94	8.11±0.072	32.0±1.50	30±0.64	80
F21	11.5%	1.08±0.01	7.47±0.36	32.0±0.9	22±1.03	84.6
F22	12.5%	1.07±1.05	6.83±1.70	32.03±1.4	9.4±0.82	88.3
F23	13.5%	1.09±0.41	8.90±0.22	32±0.11	6±0.32	87

Reproducibility of the optimized formulation

The F22 preparation with 12.5% honey concentration was identified as the optimal formulation due to its high yield (88.3%) with excellent evaluation parameters, including flow properties and friability. To confirm the reproducibility and consistency of this formulation, five additional preparations were prepared (R1-R5) on different days under the same conditions. This reproducibility study aimed to evaluate the reliability of the formulation process and ensure that the results were consistent across multiple batches. (Table 10) shows the results obtained in the evaluation of the produced granules.

Table 10. The reproducibility results of the 12.5% honey formulation are consistent and reliable.

Formula code	Bulk density	Tapped density	Hausner ratio	Carr's index	Angle of repose	Friability%	%yield
R1	0.43±0.07	0.48±0.02	1.10±0.64	6.99±0.12	32.2±0.14	9.2±0.20	88.3
R2	0.45±0.10	0.49±0.06	1.07±1.07	7.26±1.08	32.2±0.22	9.8±0.01	88.2
R3	0.46±0.18	0.50±0.06	1.06±0.11	6.28±0.31	32.0±0.21	9.5±0.13	89.02
R4	0.45±0.07	0.49±0.10	1.06±0.09	8.16±0.10	31.8±0.13	8.8±0.06	88.5
R5	0.44±1.04	0.49±0.08	1.08±0.28	7.13±1.76	32.1±0.01	10.±0.12	87.9

Discussion

The concentration of the binder solution and its type were found to be the determining factors in the wet granulation process [8]. Thinking of natural honey as a possible binder provokes its advantages over a corresponding binder like sucrose syrup. The key advantage of honey in pharmaceutics lies in its natural origin and potential for multifunctionality (e.g., sweetener, humectant). Honey has a richer nutritional value, which is considered a valuable source of minerals and vitamins [9]. This could be used in manufacturing to mask undesired taste and odor, especially in pediatric preparations.

The results of flow properties of the granules, as measured by the angle of repose, Hausner ratio, and Carr's index, were within the permissible limits for both honey and PVP preparations (Table 10). This suggests that honey-based granules can flow efficiently, making them suitable for further processing, such as tablet compression or capsule filling. The similarity in flowability between honey and PVP granules indicates that honey does not negatively impact the handling or processing of the granules, which is a critical factor in pharmaceutical manufacturing. The results of this study align with the findings of Yayehrad *et al.*, in their evaluation of Ficus gum as a natural binder in tablet formulations [10]. Both studies demonstrate that natural binders can produce granules with accepted evaluation results, making them suitable alternatives to synthetic binders like PVP.

While both binders showed similar trends in improving flowability and reducing friability, the optimal concentration of honey (12.5%) in our study yielded a granule yield of 88.3%, which was highly reproducible. The slight yield reduction at 13.5% honey concentration (Table 9, F23) indicates that 13.5% honey is a high concentration. Beyond this point, excessive honey may result in clogged mesh openings and uneven granule formation. The clogging observed at 13.5% honey concentration was likely due to the oversaturation of the mixture. Higher concentration of viscous binders such as honey can markedly increase granule size and cohesiveness [7].

Conclusion

In this study, the optimized honey formulation (12.5%) produced granules with performance metrics comparable to the high-concentration PVP formulation (3.5%). Both exhibited excellent flow and low friability. We established that 12.5% honey was the optimal concentration level for granulation, yielding the highest granule yield of 88.3%. This concentration provided the best balance between binding efficiency and granule quality, as evidenced by the good friability and flowability of the granules.

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Conflict of interests

The authors declare no conflicts of interest.

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