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Original Research

Formulation, Standardization, and Characterization of a Novel Herbal Medicine Tablet Containing Rosehip Extract

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Abstract

The fruit of *Rosa canina* L., commonly known as rosehip, has a long history of use in treating various disorders such as osteoarthritis and cardiovascular diseases. However, like many other herbal extracts, rosehip dried extract presents challenges due to its hygroscopic and sticky properties. This poses difficulties in developing solid pharmaceutical dosage forms utilizing rosehip extract. Hence, the objective of this study was to formulate and standardize a tablet containing rosehip extract. To achieve this goal, a novel wet granulation method was employed in this study to develop a tablet formulation of rosehip extract. This method utilized rosehip concentrated extract as a granulation liquid, and double granulation was employed to optimize the content of the extract. Various formulations were systematically evaluated to determine the optimal composition and ratio of excipients. Subsequently, the final formulations underwent rigorous assessment of their physicochemical properties and stability. Rosehip extract and its tablets were standardized based on ascorbic acid and total polyphenol content, using HPLC and Folin-Ciocalteu methods accordingly. To the best of our knowledge, this is the first study to report the double-wet-granulation method in a tablet formulation design along with an examination of its impact on the total polyphenol content of the extract. The key advantage of employing this method lies in its capability to incorporate liquid extract into a solid formulation, thereby facilitating the accommodation of escalating dosages of extract in each tablet. However, it is important to note that this method does come with certain limitations. Primarily, the extended formulation process necessitates prolonged exposure of active ingredients to heat and oxygen, which may potentially affect their stability and efficacy.

Keywords: Rosehip; *Rosa canina*; Rosaceae; Tablet; Quality control; Wet granulation

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Introduction

Medicinal herbs are in use for the purpose of prevention and treatment of various diseases since centuries. According to World Health Organization (WHO), 60% of the world's population depend on herbal medicines and about 80% of the population in developing countries depends almost totally on it for their primary health care needs [1]. Considering the high demand for herbal medicines, the need for formulating safe and standardized formulation of herbal medicines has grown. Standardization of herbal medicines ensures their safety, as well as medicinal and nutritive values.

Genus *Rosa* L. is one of the most widespread members of Rosaceae family with 278 species. *Rosa* fruit (rosehip) has a long history of medicinal application in various traditional medicines. It has been used for the treatment of several illnesses including ear, nose and throat problems, nausea and vomiting, and headache [2]. Alongside the traditional applications, it has exhibited various pharmacological properties. It contains high amounts of phenolic compounds, carotenoids, ascorbic acid, lycopene, folate, and fatty acids. Rosehip has antioxidant properties and inhibits free radicals. In recent studies it had shown to be beneficial for the treatment of several diseases such as rheumatoid arthritis and as lipid lowering agent, anticancer and cardiovascular protection [2].

Herbal products are presented in various dosage forms. They can be prepared in the form of a liquid, powder, capsule, or tablet [3]. Tablets are the most common formulation of oral solid pharmaceutical dosage forms [3]. Since some of the herbal extracts are composed of high amount of carbohydrates which have a high affinity with surrounding water vapor, these extracts exhibit high hygroscopic and poor compressible and flowability properties [4]. These characteristics can adversely affect the quality of the finished product, as well as the manufacturing process. Moreover, as the single dose of herbal extracts has usually a large volume, the amount of excipient needs to be limited in order to produce an herbal tablet in swallowable size [3]. Thus, selecting proper excipient and optimizing the amount of excipient is critical in the manufacturing of herbal tablets.

Rosehip extract, like many other extracts of herbal medicines, have hygroscopic and sticky properties. Furthermore, it is very difficult to be freeze dried and to be formed into powder. Due to these characteristics, it is challenging to develop a standard solid formulation using rosehip extract in pharmaceutics. The purpose of this study is to formulate and standardize oral tablet from rosehip extract in a laboratory scale and examine various quality factors. To the best of our knowledge, this is the first study to report the double-wet-granulation method in a tablet formulation design, using herbal extract. Also, first study to report the effect of the wet granulation method on the content of ascorbic acid and total polyphenol content in an herbal extract.

Materials and Methods

Materials

Rosehip was collected from Ardabil, northwest of Iran. Macroscopic examinations were performed in the pharmacognosy laboratory of the School of Pharmacy, Mashhad University of Medical Sciences. Ascorbic acid, acetonitrile, methanol, chloroform all in HPLC grade, metaphosphoric acid, gallic acid, sodium carbonate, Folin-Ciocalteu reagent, trifluoroacetic acid, sodium dihydrogen orthophosphate, were obtained from Sigma-Aldrich (Darmstadt, Germany).

Corn starch, lactose, Aerosil, magnesium stearate, ethanol (96% v/v) were obtained from Dr. Mojallali Chemical Laboratories (Tehran, Iran).

Extraction method

Extraction was carried out using the percolation method with 70% ethanol as the solvent. Initially, three hundred grams of *R. canina* fruit powder was moistened with half a liter of solvent. After an overnight soaking period, the mixture was transferred to a suitable percolator and topped up with additional solvent. Following a 24-hour period, the resulting extract underwent solvent removal using a rotary evaporator. Subsequently, the solvent-free extract was transferred to a round flask and placed in the freezer for several days to facilitate freeze-drying. The freeze dryer (Operon-55 C , Korea) was then connected to the flask. After approximately 14 days, the process was completed, resulting in the extraction of the desired compound.

Standardization of the extract

a- Evaluating the ascorbic acid content of the extract

To evaluate the amount of ascorbic acid, high performance liquid chromatography (HPLC) (Shimadzu Prominent-l Lc2030C 3D, Japan) was applied.

Condition for performing HPLC was as follow:

Column temperature 30°C, volume of injection 10 µL, flow rate 1.4 mL/min, execution time 18 minutes, storage time 3.25 minutes, wavelength 260 nm, mobile phase 0.1% trifluoroacetic acid (TFA) in distilled water in phase A and in acetonitrile in phase B.

The following standard solution was prepared for HPLC: Ascorbic acid (15 mg) was dissolved in distilled water (160 mL) and metaphosphoric acid 15% (25 mL) and made up to 250 mL with distilled water. The prepared solution was passed through a 0.45 µm Nylon filter.

The extract solution was prepared as follow:

Rosehip extract (4.5 g) was dissolved in metaphosphoric acid 15% (25 mL) and distilled water (25 mL) and made up to 250 mL with distilled water and was filtered through a 0.45 µm Nylon filter.

b- Evaluating the total polyphenol content of the extract

To evaluate the total phenol content of the extract, Folin-Ciocalteu reagent was applied and gallic acid was used as standard compound [5].

- Preparation of reagents

A Folin–Ciocalteu solution was made by diluting 1:10 (v/v) a 2 M Folin–Ciocalteu reagent with distilled water. A 1000 mg/L stock solution of gallic acid was prepared by dissolving 0.1 g of gallic acid in 100 mL of distilled water. A 20% (w/v) Na_2CO_3 solution was prepared by dissolving pure Na_2CO_3 in distilled water.

- Preparation of standard solutions, blanks and samples

Standard solutions of gallic acid were prepared at five different concentration levels (20, 40, 80, 120 and 200 mg/L) from the initial stock solution with distilled water and was used to build a calibration curve. All the standard solutions were stored at 4 °C until analysis.
The extract (125 mg) was accurately weighed and subsequently dissolved in 25 mL of distilled water. The solution was sonicated for 6 minutes to separate the phenolic compounds. The obtained solution was further filtered with filter paper to remove suspended small particles.
- Colorimetric reaction and measurements
The total polyphenol content was determined spectrophotometrically using a spectroscope (Unico UV2100, USA) and the Folin–Ciocalteu reagent, comprising phosphomolybdic acid and phosphotungstic acid. In this method, the phenolic compounds undergo oxidation in an alkaline solution, causing the acids to reduce to blue-colored tungsten oxide and molybdenum oxide [6, 7]. The intensity of the resulting coloration is directly proportional to the polyphenol concentration. To carry out the assay, Folin–Ciocalteu reagent (1 mL) was added to 6 test tubes along with distilled water (15 mL). Standard concentrations (1 mL) were then added to 5 tubes, while distilled water (1 mL) served as the blank in one tube.
After ensuring the homogenization of the contents in each test tube, sodium carbonate solution (3 mL) was added to each tube following a 6-minute interval. The tubes were once again homogenized and then incubated at 30°C for 120 minutes. Subsequently, the absorbance of both the standard (gallic acid solution) and the samples was measured at 765 nm against the blank sample. All measurements were conducted in triplicate to ensure accuracy and reliability. Finally, the results were expressed as milligrams of gallic acid per gram of the extract, providing valuable insights into the polyphenol content of the samples.
- Calculations
Standard stock solution: The concentration of gallic acid in the standard stock solution was calculated as follow:
Stock standard solution (mg/L) = M×P×(1–W) ×1000
Where M is the weight of gallic acid (g), P is the purity of gallic acid (98%), and W is the water content of gallic acid (which is determined as a decimal (1.7%)).
Calibration standard solutions: Using the gallic acid concentration of the stock standard solution, the actual concentration of each calibration standard solution was calculated as follow:
Calibration standard solution (mg/L) = (S×V)/25 mL
Where S is the concentration of standard stock solution (mg/L), and V is the volume of standard stock solution (mL).
Calibration graph was achieved using the absorbance (at 765 nm) versus concentration of calibration standards.
The total phenolic content was calculated as follow:
Total phenols (% w/w) = (V*d)/ (W*1000) *(a-b)/m*100
Where a is the absorbance of the sample test solution at 765 nm, b is the width, m is the slope of the calibration curve, W is the weight of the test substance (mg), V is the volume of the sample test solution (mL), and d is the dilution factor. The values are expressed as gallic acid equivalents.

Tablet formulation and standardization methods

Wet granulation was used to improve the physical and rheological properties of the extract, and to achieve acceptable content uniformity. Using the liquid rosehip extract as a binder in wet granulation method could overcome the rheological of the extract; however, a few amounts of the extract could be in the tablet. Double-wet-granulation is a novel method in formulating herbal tablets; Considering the physical characteristics of rosehip extract, it was applied in this study as the best way inserting the liquid extract into the tablet with a high performance. Based on the pre-formulation study, 5 different formulas were selected initially and made by double wet granulation method in small amounts. After a basic examination, the best three formulas were selected for further production and quality tests. The quality control tests were performed on granules based on United States Pharmacopeia (USP). Size distribution, density, moisture content, granule flow rate tests were applied on granules. Tablets were manufactured by tablet machine and were tested for hardness, uniformity, friability, disintegration test, and dissolution test. Ascorbic acid was selected as the initial standard, using HPLC method; however, as ascorbic acid was unstable, and the results were not reliable, total polyphenol content was applied as a second standard based on the previous research articles [8]. To analyze the total polyphenol content of the extract and tablet, Folin–Ciocalteu method [6,7] was used.

Determining the optimal tablet formulation of rosehip extract

To formulate the tablet, the liquid extract served as the granulating agent and was incorporated into the excipients. The resulting granules were then subjected to drying in an oven (0N-12G, Korea) at 39°C for 48 hours to ensure thorough desiccation. Subsequently, the granules underwent sieving through mesh size 10 to separate any adherent particles. Following this, wet granulation was repeated, with careful documentation of the exact weight and volume of the added extract at each stage.
Upon completion of the granulation process, the physical properties of the granules, including hardness, uniformity, adhesion, and pressability, were meticulously recorded. From the obtained data, three formulas were selected based on their favorable physical properties, paving the way for further development and refinement of the tablet formulation.
The ingredients of each initial formulation are shown in table 1:

Studies after granulation

- Particle size distribution of granules
The sieve method was employed to determine the particle size distribution of the granules. A total of 100 grams of granules were subjected to sieving using sieves of varying mesh sizes (10, 16, 40, and 100) for a duration of 3 minutes under vibration.
Following the sieving process, the weight difference of each sieve before and after the test was meticulously calculated. Based on these differences, the weight of the granules retained on each sieve was determined accordingly. This method facilitated the precise characterization of the particle size distribution within the granular material, providing valuable insights for further formulation

Table 1. Type and amount of ingredients used in basic tablet formulations

Ingredients	Quantity Per Tablet (%)				
	F_1	F_2	F_3	F_4	F_5
Rosehip extract (%)	50	50	50	40	50
Starch (%)	22.5	25	25	0	15
Aerosil® 200 (%)	2.5	0	0	0	0
Avicel (%)	25	25	0	0	20
Lactose (%)	0	0	25	0	0
Calcium carbonate (%)	0	0	0	60	15

optimization and quality control.

- Tapped density
The bulk and tapped density were calculated.
Based on the above results, the following parameters were calculated:

$$\%\text{Compressibility (Carr's Index)} = \frac{V0 - Vf}{V0} = \frac{\rho \text{ tapped} - \rho \text{ bulk}}{\rho \text{ tapped}}$$

$$\text{Bulkiness} = \frac{1}{\rho \text{ tapped}}$$

$$\text{Hausner's Ratio} = \frac{V0}{Vf} = \frac{\rho \text{ tapped}}{\rho \text{ bulk}}$$

The results were interpreted according to table 2.

- Moisture content
To measure the moisture content, granules (100 g) were weighed and placed in oven (39°C) for 48 h and weighed again. The moisture percentage was calculated based on the difference between primary and secondary weight.

- Flowability
The flowability of the granules was determined by a Flow-Time instrument (ERWEKA, Germany) using three parallel measurements. The flowability was expressed as the flow time (s) for a 100 mL granule sample to flow through an 8 mm orifice.

Tablet formation

To increase the lubrication of the granules, magnesium stearate (1%) was added to the granules and tablets were made with tablet pressing machine.

Tablet tests

- Hardness test
Tablets (10) were exposed to increasing force in hardness tester (ERWEKA, Germany) till they were broken or cracked. The force was applied along the radial axis of the disk.
Mean ± SD = pressure required to break the tablet

- Friability test
Tablets (20) were randomly selected, weighed, and placed in the friability tester (ERWEKA, Germany) tray (25 rpm) for 4 minutes and samples were evaluated. Any excess powder on the tablet was removed and the tablets were carefully weighed again.
Friability was calculated using the following formula:

$$\text{Friability \%} = \frac{A - B}{A} \times 100$$

A: Weight of tablets before testing
B: Weight of the tablets after the test

- Determining the amount of active substance

A) Determining the amount of ascorbic acid
HPLC (Shimadzu Prominent-l Lc2030C 3D, Japan) was used to determine the amount of ascorbic acid. In this method, 3 tablets were dissolved separately in distilled water and their insoluble materials were separated by filtration, and the amount of ascorbic acid was measured using standard ascorbic acid.

B) Determining the amount of total phenol

1) Preparation of calibration standard solutions
Gallic acid (0.1±0.1 g) was dissolved and sonicated in

Table 2. Powder / granule flow classification based on The United States Pharmacopoeia

Angle	Hausner's Ratio	Compressibility	Flow Character
25-30	1-1.11	10≥	Excellent
31-35	1.12-1.18	11-15	Good
36-40	1.19-1.25	16-20	Fair
41-45	1.26-1.34	21-25	Passable
46-55	1.35-1.45	26-31	Poor
56-65	1.46-1.59	32-37	Very poor
>66	>1.60	>38	Very very poor

water (750 mL) and was made up to 1000 mL with water.

2) Preparation of sodium carbonate solution
20 grams of sodium carbonate was poured in a 100 mL volumetric flask and was sonicated with distilled water and was brought to volume.

3) Concentration of standard solutions, blanks and samples
To prepare the standard chart, different concentrations of the gallic acid (20, 40, 80, 120, 200 mg/mL) were prepared from the initial stock solution, using distilled water. Three tablets were weighed exactly and powdered separately. The resulting powder of each was dissolved in 30 mL of distilled water and the resulting solution is made up to volume in a 50 mL volumetric flask with distilled water.

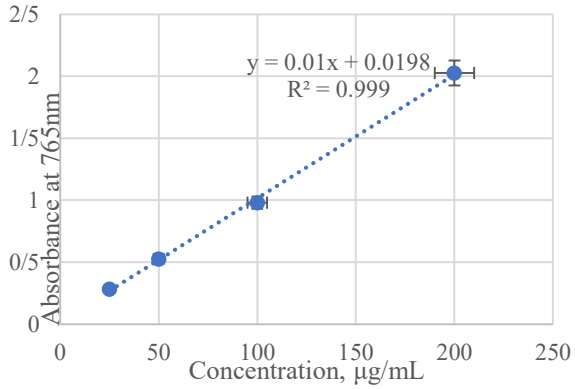
4) Colorimetric reaction
15 mL of distilled water was added to 7 tubes and 1 mL of Ciocalteu-Folin phenolic indicator was added to each. Standard concentrations (1 mL) were added to 6 tubes and 1 mL of distilled water was added as a blank to the tube which did not have the standard.
The contents of each test tube were well homogenized and after 6 minutes, 3 mL of sodium carbonate solution was added to each tube and homogenized again. Then the test tubes were placed in it for 120 minutes at a temperature of 30 °C .

5) Measurement
To measure the absorbance of the solutions, 1 mL of each sample was transferred to the cuvette and after zeroing the UV spectrophotometer with a blank, we measured the absorbance of the calibration standard solutions and the samples at 765 nm. This measurement was repeated three times.

6) Calculations
Standard stock solution: The concentration of gallic acid in the standard stock solution is calculated as follows:
Stock standard solution (mg/L) = M×P× (1–W) ×1000
where M is the weight of gallic acid in grams, P is the purity of gallic acid (98%), and W is the water content of gallic acid (which is determined as a decimal (1.7%)).
Calibration standard solutions: Using the gallic acid concentration of the stock standard solution, the actual concentration of each calibration standard solution is calculated as follows.
Calibration standard solution (mg/L) = (S×V)/25 mL
where S is the concentration of standard stock solution (mg/L) and V is the volume of standard stock solution (mL).
Calibration graph: graph absorbance at 765 nm versus concentration of calibration standards. Using the slope, y-intercept and R^2 value of gallic acid calibration curve is calculated. For the fit of the system, the R^2 value of the calibration curve should be greater than 0.99.
The total phenolic content in the test material: The total phenolic content of the test material is calculated as %w/w as follows:
Total phenols (% w/w, as is) = (V*d)/ (W*1000)*(a-b)/m*100
where a is the absorbance of the sample test solution at 765 nm, b is the width from the origin of the calibration curve, m is the slope of the calibration curve, W is the weight of the test substance in milligrams, V is the volume of the sample test solution, d is the dilution factor and 1000 is converted from mL to L and the values are expressed as gallic acid equivalents.
- Disintegration time
One tablet from each of the three formulas was placed into each of the six tubes of the disintegration apparatus (ERWEKA, Germany) and immersed in distilled water at 37 ± 2°C. Disintegration time for the last tablet in each tube was recorded. If all tablets disintegrated, the product passed. If one or two tablets didn't disintegrate, another 12 tablets were tested. To pass, at least 16 out of the total 18 tablets tested must disintegrate within the specified time frame.

- Weight
Ten tablets from each of the formulas were randomly selected and carefully weighed. The average weight of the tablets and their standard deviation were determined.

- Drug content and Dissolution tests
To ascertain the extract quantity in the tablets and conduct the dissolution test, the absorption of the extract's standard solution was employed in the ultraviolet region using a spectroscopic method with spectroscope (Unico UV2100, USA). The UV spectrum of the extract solution revealed its peak absorption at 279 nm. Subsequently, a standard curve was constructed from the extract data, and the derived equation was employed for quantifying the extract's content as well as assessing its release from the tablets in the dissolution test.
To perform the drug content test, different concentrations of the extract in distilled water (0.08, 0.4, 0.2, 1, 1.4 and 2 mg/mL) were prepared. Considering the maximum absorption in the spectrophotometer, a standard diagram was drawn. Then 3 tablets were randomly selected, ground, and dissolved in distilled water (100 mL) and the solutions were filtered. Absorption was read at the maximum wavelength and the amount of extract of each tablet was obtained using the standard equation.
To conduct the dissolution test, we utilized a dissolution test machine (Electrofarmed TD06, Iran). Three tablets were randomly selected from each formula for testing. Each tablet was placed in a flask containing 1000 mL of distilled water at 37.5°C, and the dissolution test was initiated. During the test, samples of the dissolution medium were collected at various time intervals, and an equal volume of distilled water was replenished to maintain the sink condition. The release of the extract was measured over time based on the standard equation.
To obtain the exact concentration in each sample, accounting for any loss of the active ingredient to the environment during sampling, the following formula was utilized:
$C_1=C_2+C_3\times(V_a/V_b)$
C_1 = actual drug concentration at time X
C_2 = Drug concentration read at time X
C_3 = drug concentration at time X-1
V_a = volume of liquid removed
V_b = total volume of dissolution medium
This adjustment ensured accurate measurement of the



Graph 1. Absorption of different standard concentrations of gallic acid

concentration of the extract in each sample, facilitating precise analysis of the dissolution profile.

Results

Extract analysis

Total of 900 g of the extract was obtained from 3 kg of rosehip.

- Ascorbic acid content:

The results of HPLC showed that the extract contained 32 mg/g ascorbic acid.

- Total polyphenol content:

The standard chart of gallic acid is shown in graph 1. The absorption of the methanolic extract solution (3 mg/mL) was 0.993. According to the standard chart and extract concentration, total polyphenol content of the extract was 64.82% w/w.

- Granulation results

Granules from formulas 1, 2, and 5 were identified as superior formulations due to their favorable pressability, flowability, and hardness characteristics. Conversely, formulas 3 and 4 yielded a viscous mass that was challenging to sieve and ultimately resulted in the formation of hard and non-uniform granules.

For convenience, formulas 1, 2, and 5 were designated as A, B, and C, respectively. These formulations were subsequently scaled up for further analysis.

The results of granule tests are as follows:

- Particle size distribution test

The average percentage of particles on each mesh sieve was 10 to 100. Their particle size distribution is shown in table 3.

- Density

- Moisture

The moisture content of the granules in formula A, B and C were 2.99%, 2.98% and 2.97% respectively.

- Granule flowability

Flow rates of formula A, B and C were 4.86, 5.15 and 5 (g/s) respectively.

Tablet tests

- Weight, width, hardness, content, friability

The evaluation results of tablets obtained from various formulations are summarized in table 5. All tablets exhibited weights within ± 5% of the average. Additionally, none of the tablets displayed visible cracks, splits, or breakage during the erosion test.

- Tablet standardization

The HPLC results revealed that each tablet contained 0.016 mg of ascorbic acid. Additionally, the total poly-

Table 3. Particle size distribution of each formula

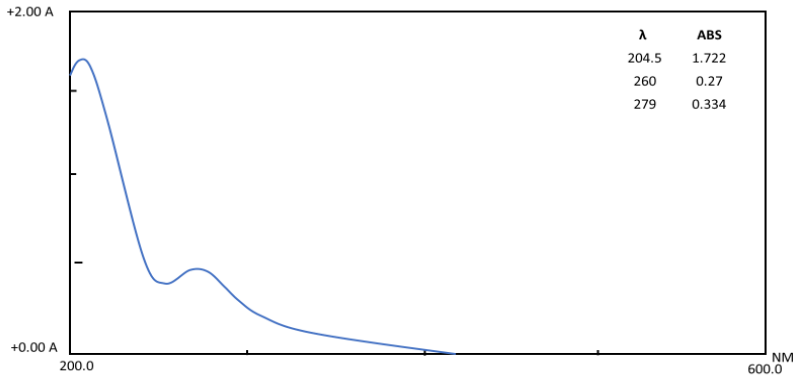
Particle size (micrometers) %	0-150	150-250	250-425	425-850	850-1200	1200-2000	2000 and more
Formula A	2	11.5	15.5	41	5	23.5	1
Formula B	3	7.5	19.5	32.5	7	28	2
Formula C	2.5	10.5	13	42.5	9.5	20.5	1

Table 4. Density related results of each formula

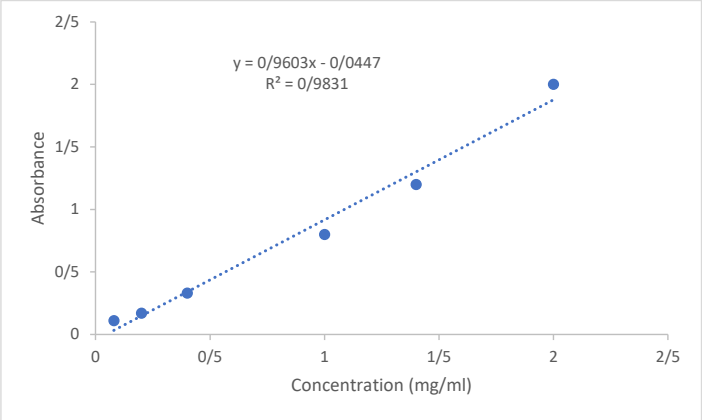
	Formula A	Formula B	Formula C
Weight of 250 mL granules (g)	99.75	112.2	103.76
Secondary volume (mL)	225	220	218
Bulk density (g/mL)	0.399	0.448	0.41
Bulk and tapped volume difference (mL)	25	30	32
Tapped density (g/mL)	0.44	0.51	0.47
%Compressibility	11.11	13.63	14.67
Bulkiness	1.27	1.96	2.12
Hausner's Ratio	1.1	1.13	1.14

Table 5. Evaluations of formulations A, B and C

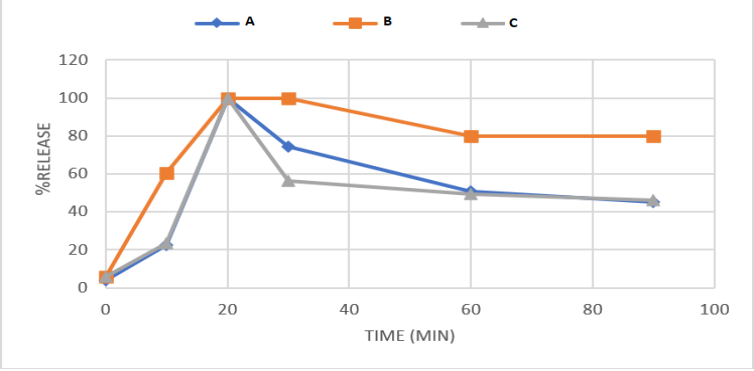
Formula	Weight (g)	Hardness (kg)	Extract content (g)	Thickness (mm)	Friability (%)	Disintegration (min)
A	0.635 ± 0.0008	5.32±0.32	0.31	5.5	0.7	6
B	0.628 ± 0.01	6.32± 0.7	0.36	5.5	1.2	8
C	0.635±0.01	5.15 ± 0.15	0.3	5.5	1.17	5



Graph 2. UVSpectrum recorded from the extract solution (10^-4 mg/ml) in wavelength ranging from 200 to 600 nm



Graph 3. Standard curve of Rosehip extract at 279 nm.



Graph 4. Comparison of the release between formulas in dissolution test of rose hip tablets

phenol content of the tablet was determined to be 26.43% w/w.

- Drug content test
Graph 2 depicts the spectrum obtained from the extract solution with a concentration of 10^-4 mg/mL, covering the wavelength range of 200 to 600 nm. It is evident from the graph that the maximum absorbance occurred at 279 nm. Utilizing this data, a standard graph was constructed, correlating the absorbance values of various extract concentrations at 279 nm (Graph 3).
Based on the absorbance value of 0.629 obtained from the solution sample of the tablet dissolved in 1000 mL of distilled water at the maximum wavelength of 279 nm, the extract content within the tablet was calculated to be 381 mg using the standard equation.

- Dissolution test
Based on the absorption levels observed at various time points and utilizing the standard graph (Graph 3), the concentration of the released extract from each tablet formulation was calculated (Graph 4).

Discussion

Given the partial efficacy, possible side effects, and delayed symptom relief associated with conventional pharmacotherapeutic approaches for numerous diseases, there has been a notable surge in the utilization of herbal medicinal products and supplements over the past three decades. Currently, over 80% of individuals worldwide rely on them as part of their primary healthcare [9]. Hence, it is imperative to intensify research efforts aimed at formulating and evaluating standardized plant-based medications, both as potential standalone treatments and as adjunctive strategies.
Granulation is among the most important unit operations in the production of oral dosage forms in pharmaceutical industry. Ideal particle characteristics in the manufacturing process include acceptable content uniformity, fluidity, shape, porosity, density, compressibility, hardness and moisture content. However, there are specific challenges in the granulation of herbal medicines due to the characteristics of row materials. Most of the herbal extracts have complex composition with diverse physicochemical properties which cause hygroscopicity and adhesiveness. Currently, the common granulation methods in the herbal medicine industry are dry granulation, spray drying granulation and wet granulation. Nevertheless, when it comes to manufacturing tablets with herbal extracts, these granulation methods encounter numerous inherent challenges, unlike their application in most chemical pharmaceuticals [10]. In this study, the fruit of *Rosa canina* (rosehip) was employed in an innovative double-wet-granulation tablet formulation technique aimed at addressing the physical properties of the extract. Various excipients were utilized to achieve optimal formulations. Selected formulations underwent rigorous standardization and characterization processes.
Ascorbic acid (vitamin C) served as the primary standard in this research, chosen based on previous studies [11,12]. According to our findings, each tablet contained approximately 300 mg of extract. As per the herbal pharmacopoeias of England and France, it was anticipated that each tablet would contain at least 0.2% (0.5 to 0.6 mg) of ascorbic acid. However, the actual amount of ascorbic acid in the tablets fell considerably below this target, a phenomenon also observed in prior research [13]. Ascorbic acid is highly susceptible to degradation from heat, humidity, and light [14,15], and the processing method can significantly influence its quantity. While wet granulation offers advantages such as improved flow and compressibility, it also presents drawbacks. This method exposes granules to heat and other environmental stresses, potentially leading to the degradation of moisture-sensitive phytochemicals like ascorbic acid. To address this issue, previous studies have assessed the levels of dihydroascorbic acid, the primary oxidation product of ascorbic acid. However, dihydroascorbic acid also rapidly degrades into inactive compounds. Accurate quantification of both ascorbic acid and dihydroascorbic acid necessitates the use of rapid high-pressure liquid chromatography-electrochemical detection (HPLC-ECD) methods [16,17]. In this study, total polyphenol content was selected as the second standard, based on insights from previous research articles [18,19]. The Folin–Ciocalteu method was employed for this purpose, known for its rapid, straightforward, and cost-effective nature, widely utilized for determining total polyphenol content [21]. This colorimetric assay relies on the reaction between polyphenolic compounds in the sample and Folin–Ciocalteu reagent, resulting in the formation of blue-colored tungsten oxides and molybdenum, detectable spectrophotometrically at 765 nm [6,7]. Compared to other analytical techniques like chromatography, the Folin–Ciocalteu method offers numerous advantages; notably, it is expeditious, easily executed, and does not necessitate expensive reagents or sophisticated instruments. However, during the process of repeated granulation and tablet formation in this study, there was an observed reduction of approximately 30% in the total polyphenol content of the extract. This decline could be attributed to the exposure of the extract to heat, light, or oxygen during the procedures.
The average extract content remained consistent across all selected formulations at 50%, and variations in filler combinations did not notably impact extract absorption in the optimal formulations. During dissolution testing, the drug release rates within the initial 20 minutes were highly comparable, with almost complete extract release observed across all three formulations within this timeframe. However, all formulations exhibited instability in aqueous environments, albeit formula B demonstrated relatively greater stability compared to the others.
The tablets exhibited uniform diameter and thickness across all formulations. Hardness and flowability measurements fell within normal ranges for all three selected formulas. Notably, tablets formulated with formula B displayed the highest hardness values compared to formulas A and C. This disparity may be attributed to the inclusion of Aerosil® 200 (fumed silica) in formula A and calcium carbonate in formula C. Previous research suggests that Aerosil can significantly impact tablet physical properties, potentially reducing tablet strength when added internally [22].

Formula B also exhibited the longest disintegration time. Faster tablet disintegration typically leads to improved drug release and absorption, thereby enhancing drug bioavailability [23, 24]. This attribute is particularly crucial for herbal tablets given the sensitivity of their phytochemicals. Interestingly, the presence of Aerosil® 200 in formula A was found to decrease the disintegration time in this study.

One of the challenges in manufacturing solid dosage forms is achieving the optimal tablet friability. Tablet friability is a critical parameter in tablet production, as excessive friability can lead to unacceptable loss of drug content during subsequent processing, storage, and handling, while low friability may compromise therapeutic effectiveness due to tablet damage. This concern is particularly significant in herbal formulations, where the composition of the entire plant mass or its extract may adversely affect friability [25].

In the friability test conducted in this study, the average weight loss of the tablets fell within the acceptable range (0.5% - 1%) across all formulas. Magnesium stearate, one of the most effective glidants [26], was added to the granules at concentrations of 1% to mitigate friction. Notably, formula A exhibited the lowest friability, potentially attributed to the presence of Aerosil® 200. Previous research has demonstrated Aerosil®'s ability to reduce friability rates [22], suggesting its suitability as an excipient for herbal tablets, especially considering that herbal extracts typically increase friability rates.

To the best of our knowledge, this study represents the first investigation into the utilization of the proposed method for formulating an herbal tablet. Additionally, it pioneers the evaluation of the impact of wet granulation on the polyphenol content of rosehip tablets.

The primary advantage of employing the double-wet granulation method in this research lies in its capability to incorporate a liquid extract into a solid formulation. Furthermore, this method offers significant potential for accommodating higher doses of extract in each tablet. While it effectively addresses certain challenges associated with herbal tablets, it does have limitations.

Foremost among these limitations is the time-consuming nature of the method, involving several steps to achieve the final product. Moreover, the prolonged formulation process exposes the ingredients to heat and oxygen for an extended duration, increasing the risk of oxidation. Consequently, some active components, such as ascorbic acid, may undergo degradation or inactivation.

Conclusion

The results of this research suggest that double-wet-granulation method can be applied to produce tablets containing liquid herbal extracts. This method can overcome the hygroscopic characteristics of the herbal extracts through the utilization of appropriate excipients. Nevertheless, further investigation is necessary to fully assess the impact of this method on the phytochemical composition and pharmacological attributes of the herbal extracts.

Conflict of Interests

There is no conflict of interest.

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