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Development and Standardization of Capsular Pharmaceutical Dosage form from Dry Extract of Ferula Tenuisecta

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Abstract

The tradition of herbal medication by plants and products of natural origin in the treatment of various diseases exists thousands of years. Currently, despite the achievements of chemistry and biotechnology, the relevance and popularity of the herbal medicine is quite high. The therapeutic effect peculiarity of the medications from herbal medicinal raw materials is that the therapeutic effect does not occur immediately and is not always obvious, as in case of medications producted by chemical synthesis. However, medications which contain biologically active substances (BAS) of plant origin, unlike synthetic ones, do not cause allergies, are low-toxic, have a favorable effect on the body, and do not have side effects during the continuous use.

Keywords: Capsule, average, herbal medicine, extract, ferula.

Introduction

Ferulatenuisecta (lat. *Fērulatenuisēcta*) is popular in folk medicine of Central Asia, the medicinal raw material of which is the milky juice of roots, gums and resin[1]. It acts as a antifatigue, antibacterial, anti-inflammatory, antifatigue and antitumor medication. One can use ferula both internally and externally. One takes an infusion for internal use. Ferula can be used for internal use in order to debride a wound, and it is also can be used to lubricate wounds, tumors, boils, and trophic ulcers. It is possible to make compresses by a warmed bandage on the sore spot.

The Institute of the Chemistry of Plant Substances named acad. S. Yu. Yunusov of the Academy of Sciences of the Republic of Uzbekistan has developed a technology for the sum determination of terpene compounds and then the production of a dry extract. We found the estrogenic activity within the screening study of extracts, sum and separate compounds of Ferulatenuisecta.

Materials and Method

In order to make Summary in respect to the composition and technology of capsules of Ferulatenuisecta dry extract, we put under study the main physical, chemical and technological properties of the substance samples . These properties are interrelated and can influence the process of high-quality capsules production with the necessary therapeutic effect in a certain way. The substance-powder of Ferulatenuisecta dry extract and the encapsulated mass were subject to physical, chemical and technological research. From the technological properties of the dry extract, the fractional composition, porosity, flowability, tap density, angle of natural slope, compressibility, compression ratio and residual moisture were under study.

The research findings of dry extract technological properties showed unsatisfactory values of flowability and angle of natural slope, which will obviously have a negative impact on the filling process of capsules, so we had the task to improve these indicators by the optimal selection of the excipients and technological process.

Table 1: The results of the technological properties study in relation to dry extract of Ferulatenuisecta

№	The indicators under study	UOM	Results
1.	**Fractional Composition:** +1000 -1000 + 500 - 500 + 250 - 250 + 150 - 150 +125 - 125	µm, %	 2.2 20.1 45.3 12.4 11.6 8.4
3.	Tap density	kg/m^3	452,00±2,07
4.	Flowability	10^{-3} kg/s	0,55±0,83
5.	Angle of natural slope	degree	72.00
6.	Compressibility	H	70,0±5,0
7.	Residual Moisture (70^{0}C)	%	5.00

In case of capsules development[2], where dry extract is the main substance (which, as a rule, does not have a satisfactory value of the flowability index), one can use the method of pre-wet granulation in order to select the optimal technology, as well as to improve the technological indicators. As for the completeness and objectivity of the paper, we decided to select the optimal composition and technology of the capsular pharmaceutical dosage form.

As the principal vehicle, we selected microcrystalline cellulose (MCC)[3] of the following brands, "MCC-101" and "MCC-102" these MCC brands are most popular in the production of medicines among domestic pharmaceutical enterprises. MCC-102 is superior to MCC-101 by its technological parameters, which makes it possible to use it for tableting by direct compression, but from an economic perspective, the price of MCC-102 is 50% higher than MCC-101. Also, potato and corn starches were used as vehicle, both of these excipients also have leavening property, which in turn can improve the flowability index[4]. As excipients we also used: lactose monohydrate (as a moisture-absorbing and adsorbing agent), aerosil[5] (as a fluidity-enhancing and adsorbing agent), talc, magnesium stearate, calcium stearate (as antifriction substances that improve the flowability).

In addition, we used the following excipients as for the pre-wet granulation method: ethyl alcohol (various concentrations), starch paste (various concentrations) and purified water.

After that, we made a number of experiments on the composition selection with the subsequent preparation of various masses in order to fill the capsules. The following table shows the most optimal compositions of encapsulated masses in terms of both technological indicators and the highest economic profitability.

Table 2: The compositions of capsules selected with the use of various excipients

Name of medications and excipients	Quantity of medications and excipients, mg				
	1	2	3	4	5
Dry extract	40	40	40	40	40
MCC-102	295				
MCC-101		295	200	195	198
Corn starch			155		155
Potato starch	60	60			
Lactose				155	
Talc				5	2
Aerosil	2	2	2	2	2
Magnesium stearate	3	3	3	3	3
Average weight	400	400	400	400	400

In the selection of the encapsulated mass various compositions and their subsequent preparation, we have consistently studied the technological properties obtained by both dry blending and pre-granulation method. The research results of the encapsulated mass technological properties you can find in table 3.

We used purified water; ethyl alcohol of 40, 70, 96% concentrations; 3, 5, 10% starch paste as moistening agent. We obtained granulated masses with each binding agent. The results of the experiments showed that the most optimal binding agent was 5% starch paste.

Table 3: The research results of the encapsulated masses technological properties obtained with various excipients

№	Verifiable indicators	Units of Measure	Compositions				
			1	2	3	4	5
1	Fractional composition, μm	%					
	+1000		-	-	-	-	-
	-1000 +500		0.60	0.49	8.20	6.20	6.40
	-500 +250		3.40	3.51	12.10	9.55	9.55
	-250 +150		10.15	9.45	12.75	18.46	18.7
	-150 +125		65.45	72.14	54.25	47.24	47.0
	-125		20.4	14.41	12.7	18.55	18.35
2	Flow ability	10^{-3} kg/s	6,4±1,1	3,8±0,2	2,6±0,1	2,8±0,2	6,7±0,2
3	Angle of natural slope	degree.	40	58	60	65	45
4	Tap density	kg/m^3	560±0,8	520±0,8	720±1,8	638±3,1	670±2,1
5	Residual moisture (70°C)	%	4	3.5	4-5	4-5	3

The production of granules by pre-granulation worked in accordance with the following method: the substance and excipients separately passed through a sieve with a hole diameter of 150 μm. We weigh the desired amount, after we mix the substance and excipients for 40 minutes, after we granulate them by wet granulation in the desired amount of starch paste as a binding agent. We line the resulted wet mass by a thin layer on a baking tray with parchment paper and place it in exsiccator, we dry it at a temperature of 60-70°C up to the optimal relative humidity of the mass (3.6-3.0%). We pass the dried mass through a sieve with a hole diameter of 1000 μm by pressing, thus we form granules. We powder the resulted prepared granules with magnesium stearate, talc and aerosil pre-sifted through a sieve with a hole size of 125 μm. The resulted mass goes to the capsule filling process.

On the basis of technological properties research results, we have proposed the most optimal composition of capsules with Ferulatenuisecta dry extract:

Dry extract	– 40 mg
MCC-101	– 198 mg
Corn starch	– 155 mg
Talc	– 2 mg
Aerosil	– 2 mg
Magnesium stearate	– 3 mg
Average weight	– 400 mg

The next stage of our research was to study the quality indicators of capsules with Ferulatenuisecta dry extract and encapsulated mass by the method given in the literature.

Description: Hard gelatine capsules of bright red color, with volume №1. The encapsulated mass in the form of granules with adelomorphous shape, of brown color.

Identification: The ultraviolet spectrum of the solution obtained for quantitation within the range from 230 nm to 290 nm has a maximum absorption at (260±2) nm.

Shake 0.4 g of the powder poured from the capsules with 8 ml of glacial acetic acid for 5 minutes and filter it through a paper filter (GOST 12026-76). Add 0.2 ml of vanillin solution to sulfuric acid to the filtrate, and a blue-green staining appears (a sesquiterpene ferutinin residue).

Weighing of the average mass. In order to weigh the average mass, we weigh 20 unopened capsules together and determine the average weight of the capsule. Then weigh each capsule separately and compare it with the average weight. The deviation of the each capsule mass should not exceed±10% of the average mass. Then carefully open the same 20 capsules, remove the contents

as completely as possible and weigh each shell. For soft capsules with liquid or pasty contents, we wash the shell with ether or other suitable solvent before weighing with the following air removal of the solvent. Determine the average mass of the capsule contents. Unless there are no any specified instructions in the individual monographs, the mass deviation of each capsule contents from the average mass should not exceed±10%, with the exception of two capsules, in which a deviation is possible of up to±25. If more than 2 capsules, but not more than 6 have deviations from the average weight within the range of 10 to 25%, then we determine the contents of each capsule and the average weight of the contents of 60 capsules with 40 capsules in addition. No more than six capsules out of 60 can have deviations from the average weight of more than±10% and there should not be any capsules that have a deviation in the mass of the contents of more than±25%. We use the contents of 20 or 60 capsules for quantitation of medicinal substances and other indicators under individual monographs.

Disintegration: One can determine it by a special laboratory identifier.[6] The device design consists of a "basket", a vial with a volume of 1 l (for liquid), a thermal device that maintains the temperature of the liquid within (37±2)°C, an Electromechanical device that supplies the basket with a reciprocating motion by a frequency of 28 to 32 cycles per 1 min.

The main part of the device consists of a rigid basket with a mesh bottom which supports six cylindrical glass tubes, whose length is (75.5 - 79.5) mm, internal diameter is (20.7-23) mm and wall thickness is (1.0 - 2.8) mm. The glass tubes locate vertically and two plastic plates hold them (at the top and bottom) The parameters of plates are: a diameter (88-92) mm, thickness (5-8.5) mm, it has six holes with diameter (22-26) mm. The holes are equidistant from the center of the plate and from each other. A square grid with cells of size (1,8 - 2,2) mm and a stainless steel wire of diameter (0,57 - 0,66) mm fixes to the lower plane of the plate. The rods hold the plates in vertical position along the entire circumference. Another rod fixes in the center of the plate upper plane, which allows you to attach the basket to a mechanical device. You can raise and lower the basket by it. The time of movement up and down should be the same.

We select 16-18 capsules for the test. One sample is in each tube. We lower the basket into a container with liquid and turn on the device. At the end of the specified time, we withdraw the basket. Examine the state of the samples. All the tested samples must completely disintegrate. If 1-2 capsules do not fall to pieces, we repeat the test with the remaining samples. At least 16 of the 18 selected samples must completely disintegrate.

One can consider that sample have passed the test if it leaves no residue, or a residue is in the form of a soft mass that falls in parts at the slightest touch of a glass stick.

The findings: the tested capsules completely disintegrate within 14 minutes.

Quantitation: We place about 0.4 g (precisely weighed amount) the powder poured from the capsules in a measuring flask with a capacity of 100 ml, add 80 ml of 96% alcohol and shake for 10 min., then bring the volume of the solution with the same solvent to the mark, filter it through a paper filter (blue tape), discarding the first 10 ml of filtrate. We transfer 1 ml of filtrate to a measuring flask with a capacity of 25 ml, bring the volume of the solution with 96% ethyl alcohol up to the mark and mix. We measure the optical density of the resulting solution by a spectrophotometer at a wavelength of 260 nm in a cuvette with a layer thickness of 10 mm. We use 96% ethyl alcohol as a reference solution.

At the same time, we measure the optical density of the ferulen work standard solution. We calculate the content of ferulen in one capsule, in grams (X) by the formula:

$$X = \frac{D_1 a_0 * 100 * 1 * 3 * b}{D_0 * a_1 * 100 * 1 * 6} = \frac{D_1 * a_0 * b}{D_0 * a_1 * 2}$$

Where:

D_0 is the optical density of the ferulene work standard solution;

D_1-optical density of the test solution;

a_0 - dose weight of the ferulen work standard, in grams;

a_1 - dose weight of the powder poured from the capsules, in grams;

b-the average weight of one capsule in grams.

The content of ferulen in one capsule should be from 0.036 g to 0.0044 g (in terms of feerutinin from 0.009 g to 0.011 g) with count of one capsule average weight.

Table 4: The quantitation metrological description of capsules with dry extract of Ferulatenuisecta

Series	Dose weight, g	Findings		Metrological description
		By dose weight, g	In one capsule, g	
011117	0.400	0.160	0.040	X_{avg} = 0,159 t(95%,4)=2,78 S^2 = 0,00000525 S = 0,00229±DX = 0,00636±DE = 4,006 P = 95
021117	0.405	0.158	0.039	
031117	0.410	0.156	0.038	
041117	0.41	0.162	0.039	
051117	0.40	0.160	0.040	

Note: Preparation of the solution with the work standard of ferulen. We place about 0.04 g (precisely weighed amount) of ferulene (in terms of ferutinin 0.01 g) in a 100 ml volumetric flask, add 80 ml of 96% alcohol and dissolve with continuous stirring. Then we bring the solution volume with the same solvent to the mark and mix. We transfer 3 ml of the resulted solution to a measuring flask with a capacity of 25 ml, bring the volume of the solution with 96% alcohol to the mark and mix. The solution must be freshly prepared.

Packaging: 10 capsules in a contour–cell package in accordance with GOST 64-074-91 (All-Union standard) from polyvinyl chloride film in accordance with GOST 25250-88 or imported and printed lacquered aluminum foil in accordance with TU 48-21-270-78 or imported or 10, 20, 30, 50 and 100 in polymer vials (banks) in accordance with GOST 64-15390981-02:2003 from low-pressure polyethylene in accordance with GOST 16338-85E or high-pressure polyethylene in accordance with GOST 16337-77, the vials must have labels made of label paper by GOST 7625-86e or writing paper by GOST 18510-87e.[7]

We place packs, contour cell packages by 1 [no. 10(1x10)], by 2 [no. 20(2x10)], by 3 [no. 30(3x10)] pieces together with the instructions for use in a pack (pencil case) of box cardboard in accordance with GOST 7933-89E or other imported and with packing lists on accordance with OST 64-7-382-84 placed in a box of box cardboard in accordance with GOST 8273-75 or bagged by GOST 2228-81E. The boxes or stops are pasted with a parcel made of wrapping paper by GOST 8273-75 or tied with cotton threads in accordance with GOST 6309-87 or twine made of bast fibers by GOST 17308-88, the ends of which are pasted with a label made of label paper in accordance with GOST 7625-86E or writing paper in accordance with GOST 18510-87E.

Table 5: The research results of technological properties in relation to encapsulated mass and quality indicators of capsules

№	Verifiable indicators	Units of Measure	Results
1	**Fractional composition, μm** +1000 -1000 +500 -500 +250 -250 +150 -150 +125 -125	%	- 6.40 9.55 18.7 47.0 18.35
2	Flowability	10^{-3}kg/s	6,7±0,2
3	Angle of natural slope	degree.	45
4	Tap density	kg/m^3	670±2,1
5	Residual Moisture (70°C)	%	3
6 7 8 9 10	Appearance Authenticity Deviation from the average weight of capsules Disintegration Quantitation (in terms of ferulinin)	g, % min. g	Red capsules with volume № 1 respectively 0,394±0,13 14 ± 2,32 0,009-0,011

The identification of stability and capsules shelf life. The purpose of stability investigation is to obtain data on changes over time in the quality of the medication under the influence of various environmental factors, such as temperature, humidity and light, as well as to establish the frequency of repeated studies of the active substance or the shelf life of the medication and recommended storage conditions[8].

The stability tests of the Pharmaceutical Dosage Form must be in the intended packaging for presentation on the market (including, if necessary, any secondary packaging and container labels).

The use of rational packaging[9] is the main way to prevent a decrease in the quality of encapsulated medications in storage. Therefore, the type selection of packaging and packaging materials is individual in each case in accordance with the physical and chemical properties of the substances within the capsules.

One of the most important requirements for packaging materials is the protection of capsules from light, atmospheric moisture, air oxygen, and microbial contamination. Today, we use the traditional packaging materials such as paper, cardboard, metal, and glass for capsule packaging. Along with the traditional materials, film packages made of cellophane, polyethylene, polystyrene, polypropylene, polyvinyl chloride and various combined films on the basis of them are popular. The most promising film contour packages, which are produced on the basis of combined materials by the method of thermal welding, are strip pack (tape) and cellular pack (blister).

In order to make tape packaging it is popular to use laminated cellophane tape in various combinations, aluminum foil, laminated paper, laminated polyester or nylon polymer film. One can make packaging by heat welding of two-placed materials. The special machines make such packs. As a thermoforming film, hard (non-plasticized) or weakly plasticized polyvinyl chloride (PVC) with a thickness of 0.2-0.35 mm or more is most popular for usage. PVC film is well formed and heat-bonded with various materials (foil, paper, cardboard, covered with a thermolak layer). The film covering by polyvinyl chloride or ethylene halogenation reduces gas and vapor permeability. For hygroscopic medicines, we recommend to use polypropylene, but it is more difficult to form. In addition, it is more tough than PVC. Polystyrene is also well formed, but is unpopular due to its high water permeability. In order to close the cells, aluminum foil is quite popular. On the inside, it is covered with glue or thermal adhesive film, on the outside-with varnish. Aluminum foil is impervious to water vapor and gases, well protects the medications from the fragrance permeation. The packaging, one layer of which is aluminum foil, provides high tightness.

The main function of containers, packaging and capping is to isolate a separate dosage (portion) of a medication not only from other dosages of the same medical product, but also from the effects of so-called environmental factors: light, atmospheric air pressure, atmospheric natural gases and vapors, as well as from the evaporation into the surrounding atmosphere of other medical products, chemicals and products that one stores in the same or in neighboring rooms. In other words, one determines the suitability of a package by four properties: protection, safety, compatibility, and performance (functioning and/or delivery of medicines). In case of the packaging/capping system assessment, we must consider the following factors: design materials of the packaging/capping device; surface treatment and/or technological additives; active ingredients and vehicles that are part of the Pharmaceutical Dosage Form; sterilization and/or other similar processes; finally, storage conditions.

Storage conditions have a great influence on the stability of medicinal substances within capsules and on their physical and chemical parameters.

An increase in air temperature and the effect of direct sunlight have a negative impact on the quality of capsules. Therefore, one stores the capsules at room temperature in a dry, protected from light place.

Stability tests should include studies of such characteristics in respect to the finished medicinal product that are subject to changes during storage and may reasonably affect quality, safety and/or efficacy. One should study physical, chemical, biological and microbiological properties (in accordance with the specific situation). Thus, the study of medical product stability is an additional source for development and improvement of the requirements that determine the quality of medical products.

One stores the hard gelatine capsules with a dry extract of the Ferulatenuisecta at room temperature (20±5)°C, humidity (60±5)%. These conditions correspond to the natural method of storage, the research duration is1 year with intermediate quality checks every 6 months the research continues. The findings show the value of the verifiable indicators within the normal range, and one can also note that the various containers and packaging materials selected for capsules storage ensure safe storage and stability of the medical product. Thus, we can recommend the packaging materials used in the experiments for further use.

Also, one of the most popular research method within the stability identification of medical products is the method of "accelerated ageing". The essence of the method is to increase the storage temperature at the expense of a thermostat usage, and in the presence

of more advanced equipment that can also control humidity indicators and automate the process, one can achieve more accurate research results. In accordance with the experiments results, the optimal temperature for the capsules was 40°C, as at the storage temperature of 50–60°C, the quantitative indicators of the capsules showed some changes. The packaged capsules were put in a thermostat (40°C) and every 46 days (corresponding to 6 months of storage at room temperature) passed the quality indicators examination. As a result of the experiments, the shelf life of capsules with dry extract of Ferulatenuisecta was 184 days (on the basis of 2 year storage at room temperature), the results are in the table.

Table 6: The capsules shelf life identification by natural storage

Types of packaging GOST, OST, TU	Verifiable indicators	Primary results	Shelf life, months	
			6	12
1	2	3	4	5
Plastic bottles with screw cap (64-20-8780) brown glass vials (OST 64-2-71-80)	Appearance Average weight, g Disintegration, min. Authenticity Amount of ferulinin, g	Respectively 0.4010 14 Respectively 0.010	Respectively 0.4011 14.30 Respectively 0.010	Respectively 0.4012 15 Respectively 0.0098
Brown glass vials with plastic screw caps (64-287-81)	Appearance Average weight, g Disintegration, min. Authenticity Amount of ferulinin, g	Respectively 0.4012 14 Respectively 0.009	Respectively 0.4013 14.25 Respectively 0.009	Respectively 0.4015 14.50 Respectively 0.009
Contour-cell packaging materials (OST 64-744-6-81)	Appearance Average weight, g Disintegration, min. Authenticity Amount of ferulinin, g	Respectively 0.4011 14 Respectively 0.009	Respectively 0.4017 14.15 Respectively 0.009	Respectively 0.4019 14.30 Respectively 0.0087

Conclusions

One selected the optimal composition of the encapsulated mass and the subsequent study of the technological properties, the findings showed an improvement in the flowability and angle of natural slope after the addition of excipients and pre-wet granulation. Also, on the basis of the obtained optimal composition, the average weight of capsules was 0.4 g and the size of the most optimal gelatin capsule in accordance with the volume № 1.

There were complex experimental studies in respect to the main quality indicators of developed capsules in accordance with the State Pharmacopoeia of XI edition, notably: organoleptic properties, average mass, mass uniformity, disintegration, authenticity, quantitation. One determined the shelf life and stability of capsules by the method of "accelerated aging" and natural storage[10].

We selected the packaging and storage conditions for the received capsules, and the shelf life of the capsules was 2 years.

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