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Sambucus nigra (L.) liophylised extract as source of direct compression tablets obtaining

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Abstract The aim of this paper is the valorization of a 10 % anthocyanins elderberries lyophilized extract standardized as cyanidin-3-glucoside in lozenges obtained by direct compression and quality lozenges evaluation according to Romanian and European pharmacopoeia tests. The resulting lozenges with a 600 mg concentration of a 10 % anthocyanins elderberries lyophilized extract standardized as cyanidin-3-glucoside were evaluated using the following tests: appearance and mass uniformity (20 lozenges) disintegration time (6 lozenges), hardness (10 lozenges), anthocyanins assay expressed as cyanidin-3-glucoside using a spectrometric method at pH differential values. The results are expressed as means± standard deviation. The tablets for the two formulas have the same appearance (flat, round, colored in purple – red, non gritty), the dimensional characteristics (height, thickness) are different, average mass complies the pharmacopoeia standards. The lozenges from formula 2 have a higher resistance (215.7 N) and a lower disintegration time (11 min.) according to the official recommended values, due to differences from carbopol polymers differences in properties at the same concentration used in the two formulas. Using the direct compressible products described in this study, the direct compression technique can be easily applied for the manufacture of lozenges, thus ensuring their stability by avoiding heat and humidity factors during the manufacturing process. The resulting lozenges from formula 1 respect the quality specifications provided by the Romanian Pharmacopoeia Xth edition, the European Pharmacopoeia. The lozenges presented a high mechanical resistance (110 N) and a good disintegration time (15 min.)

Keywords: elderberries lyophilized extract, lozenges, direct compression, official quality tests.

1. Introduction

Sambucus nigra L., *(Caprifoliaceae)* the species on which the majority of scientific research has been conducted, is a deciduous tree growing to 10 m (32 ft) with cream-white flowers and blue-black berries.

The flowers, leaves, and berries are rich in flavonoids, vitamins C and P, and B_1, B_2, and B6. Elder berry contains the flavonoid glycosides, hyperoside, isoquercitrin, and rutin, and anthocyanins glycosides chrysanthemin, sambucin, and sambucyanin. There is also approximately 0.01% essential oil containing 34 identified compounds. Elderberry preparations are made from either the fresh or dried fruit.

Elderberry extract inhibits hemagglutination produced by the influenza viruses in humans, increases production of inflammatory and anti-inflammatory cytokines in humans.

A 4% elderberry extract, obtained by extraction with 70% ethanol and vacuum-concentrated to 50-60% content dry matter enhances activity of lysosomal enzymes; reduces production of lipoxygenation products; reduces myeloperoxidase activity.

Elderberry extract exhibits oxygen radical absorbing capacity (ORAC) *in vitro* comparable to cranberry (*Vaccinium macrocarpon* Aiton) and raspberry seed (*Rubus idaeus*), but less than strawberry powder (*Fragaria* sp.), grape seed proanthocyanidin powder (*Vitis vinifera*), wild

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blueberry and blueberry extracts (*Vaccinium* spp.) [1 - 3].

To increase the therapeutic performance of the tablets in their formulation, in addition to the active substance using different adjuvants, which are designed to facilitate the release of active substance, while contributing to the stability of the products. In this respect we have been proposed formulas in table I to obtain oral tablets uncoated, lozenges.

Lozenges are tablets that dissolve or disintegrate slowly in the mouth to release drug into the saliva.

They are easy to administer to pediatric and geriatric patients and are useful for extending drug form retention within the oral cavity. They usually contain one or more ingredient in a sweetened flavored base.

Drug delivery can be either for local administration in the mouth, such as anaesthetics, antiseptics, and antimicrobials or for systemic effects if the drug is well absorbed through the buccal lining or is swallowed. More traditional drugs used in this dosage form include phenol, sodium phenolate, benzocaine, and cetylpyridinium chloride. Decongestants and antitussives are in many over - the - counter (OTC) lozenge formulations, and there are also lozenges that contain nicotine (as bitartrate salt or as nicotine polac-rilex resin), flurbiprofen (Strefen), or mucin for treatment of dry mouth (A.S Saliva Orthana) [4,5] .

This type of tablet formulation involves the combination of ingredients to ensure a pleasant, appropriate mechanical strength and disintegration time prolonged (15-30 minutes).

Lozenges can be diamond shaped, biconvex, weight varies from 1.5 to 4 g,

Materials necessary to get compressed tablets lozenges are: diluants, binders, lubricants, flavorings and colorings. The most used method of obtaining lozenges is direct compression, which will require the use of direct compression excipients suitable for this type of process [4 - 6].

2. Experimental

The raw material for lozenges obtaining was a dark-red powder of spherical particles, with a uniform particle size, and a slight characteristic odor. This powder is sensitive to oxygen, light, heat and moisture.

The product is highly resistant to pressure, contains 10% lyophilized anthocyanins elderberries extract expressed as cyaniding -3 –glucoside and was produced by ARTEMIS Intenational Ltd. [7].

Lozenges can be made by molding or by compression at high pressures, often following wet granulation, resulting in a mechanically strong tablet that can dissolve in the mouth.

On the direct compression forms of the drug the following pharmacotechnical determinations were performed [6, 8 - 10]:

- flow time and speed – using timing the flowing of a certain quantity of material through a standard diameter orifice (Erweka GDT apparatus);
- tapping behavior (Vankel Tap Density tester device);
- Haussner ratio and Carr index (applying the formula mentioned in the literature);
- humidity content (halogen HR 73 Mettler Toledo humidity analyser).

For direct compression we used the excipients of pharmaceutical degree represented by, Sucrose direct compressible, carbopol 71G; carbopol 934, lactose direct compressible 11 (BASF, Germany); and magnesium stearate (Peter Greven, Netherlands). Carbopol® 71G NF polymer was designed for use in oral solid dosage applications. Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol.

The unique feature of Carbopol 71G NF polymer is its granular physical form. In contrast, all other Carbopol® polymers are supplied in the powder form. Carbopol 71G NF polymer is a free-flowing granular form of Carbopol® 971P NF polymer, for use in direct compression formulations.

The resulting granules are free flowable, have increased bulk density, and contain minimal amounts of very small particles that can cause dusting and/or static adherence compared to the powder polymer.

The lozenges were obtained by direct compression using a Korsch excentric machine with 12 mm-diameter punches. The formulation for the lozenges is shown in **Table 1.**

Table 1. Elderberries lyophilized extract lozenges formulation

Ingredients	**Formulas (mg / tablet)**	
	Formula 1	**Formula 2**
Elderberries e lyophilized extract 10%	600	600
Lactose DCL 11	172	172
Sucrose DC	700	700
Carbomer 934	-	18
Carbomer G 71	18	-
Magnesium stearate	10	10
Total mass (mg)	1500	

The preparation of the lozenges followed the next steps: the components of each formulation were weighed, sieved and mixed for 5 minutes in a cubic mixer, then they were compressed with an average compression force of 18 kN, using an excentric machine with 12 mm-diameter punches.

The lozenges were evaluated using the following tests:

1. The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking [6, 9].

2. Uniformity of weight

20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity [6, 9].

3. Disintegration time

The test was carried out on 6 tablets using PTZ S tablet apparatus, distilled water at 37ºC ± 2ºC as a disintegration media and the time in minutes taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured [6, 9].

4. Hardness/

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of 10 tablets was measured using Pharma PTB Tablet Hardness Tester. Results are expressed as mean ± S.D. [6, 9].

The size and shape of the tablet were dwtermined on 10 tablets using the apparatus above described.

5. Total monomeric anthocyanins (ACY) determination

ACY were determined using the pH differential method [11, 12]. Absorbance was measured at 520 and 700 nm using a Jasco V-630 spectophotometer [12, 13].

Monomeric anthocyanin pigments reversibly change color with a change in pH; the colored oxonium form exists at pH 1.0, and the colorless hemiketal form predominates at pH 4.5. The difference in the absorbance of the pigments at 520 nm is proportional to the pigment concentration.

ACY were expressed as cyanidin-3-glucoside (cyd-glu) and calculated using the formula:

Anthocyanin pigment (cyanidin-3-glucoside equivalents, mg/L) =

$$\frac{A.\bullet MW.\bullet .DF.\bullet 10^3}{\varepsilon.\bullet .1} \quad (1)$$

Where:

A = (A520nm – A 700nm) pH 1.0 – (A520nm – A700nm) pH 4.5;

MW (molecular weight) = 449.2 g/mol for cyanidin-3-glucoside (cyd-3-glu);

DF = dilution factor established in D;

l = pathlength in cm;

ε =molar extinction coefficient of 26.900 L cm^{-1},

10^3 = factor for conversion from g to mg.

3. Results and discussion

The resulting values for the flow time show that the materials have low flow properties. The bulk and tap density values allowed us to calculate the Hausner ratio and Carr index, these values indicating a good compressing behavior.

The humidity content is within limits that do not influence the stability of the products. The results are shown in **Table 2.**

Table 2. The pharmacotechnical properties of the studied DC materials

Characteristics	**Elderberries lyophilized extract 10%**
Flow time (sec)	9.9
Bulk density (g/cm^3)	0.5029
Tap density (g/cm^3)	0.6860
Haussner balance	1.364
Carr index (%)	26.69
Humidity content (%)	1.23

The experimental results of the tests performed on these lozenges are shown in **Table 3.**

The tablets for the two formulas have the same appearance (flat, round, colored in purple – red, non gritty), the dimensional characteristics (height, thickness) are different, average mass complies the pharmacopoeia standards.

Table 3. The experimental results of the quality and quantity tests performed on Elderberries lyophilized extract 10% lozenges

Tested Parameters	**Results (Means± S. D.)**	
	Formula 1	**Formula 2**
Appearance	Flat, round, purple - red colored	
Diameter (mm)	12	13.13
Height (mm)	5.53	5.51
Average mass (mg)	1500±5%	1492±5%
Anthocyanins (mg/tablet)	600 mg ±5%	595 mg ±5%
Hardness (N)	111 ± 10%	215.7± 10%
Disintegration time (min.)	15	11

The lozenges from formula 2 have a higher resistance (215.7 N) and a lower disintegration time (11 min.) according to the official recommended values, due to differences from carbopol polymers differences in properties at the same concentration used in the two formulas.

4. Conclusions

Using the direct compressible products described in this study, the direct compression technique can be easily applied for the manufacture of lozenges, thus ensuring their stability by avoiding heat and humidity factors during the manufacturing process.

The resulting lozenges from formula 1 respect the quality specifications provided by the Romanian Pharmacopoeia Xth edition, the European Pharmacopoeia.

The lozenges presented a high mechanical resistance (110 N) and a good disintegration time (15 min.)

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