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PREPARATION OF A TRADITIONAL POLY HERBAL PRODUCT AND STABILITY ASSESSMENT OF THE DOSAGE FORM

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ABSTRACT: *"Soda"* is one of the humors in the body which should be in normal level for being healthy. If *"soda"* increases in the body, some undesirable symptoms appear. In order to eliminate the excess *"soda",* at first it should be maturated. There are different formulations in Iranian traditional medicine references as *"Monzig-e-soda"* which is a way of maturation of black bile. In one of the references, the aqueous extract of *Cordia mixa*, *Glycyrrhiza glabra*, *Adiantum cappilus-veneris*, *Foeniculum vulgare*, *Fumaria* spp, *Lavandula angustifolia*, *Echium amoenum*, *Melissa officinalis* and *Ziziphus jujuba* is prepared as decoction. In the present investigation, the capsule form of the plants was prepared and its stability was assessed. The mentioned species were mixed in ratio of 2.4:1.5:1:1:1:1:1:2, respectively and extracted with water (1:10) in 90 °C, 2h. The aqueous extract was dried and packaged in capsules 500 mg. In order to assess the stability of capsules, they were divided into two groups: group 1 were placed in 30 °C and room humidity for 12 months (long- term stability) and group 2 were put in 40 °C and 75% humidity for 6 months (accelerated stability). Sampling was performed every 2 months and total phenolic compounds, mucilage content and microbial levels were determined in each sample. The results showed no significant changes in total phenolics and mucilage contents of the capsules during accelerated tests. Microbial tests were in agreements with references. For estimating expiration date for the product by using Y=2X formula, two years stability could be predicted.

INTRODUCTION: According to Iranian traditional medicine (ITM), the body consists of four humors including blood, phlegm, yellow bile and black bile that each of them has a certain temperament. When the humors are in balance, the body is healthy while, unbalance humors can cause illness [1 - 4].

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Among these four humors, black bile (traditionally named "*soda"*) is the heaviest one and in fact it is the blood sediments which results from the metabolism of the blood. "*Soda"* is responsible for nourishing the spleen, bone, cartilage and tendons. Other roles include strengthening the stomach, stimulating appetite, causing blood concentration as well as reducing blood circulation [5].

The excess of "*soda"* production in the body can cause related symptoms. These symptoms can be divided into mental and physical symptoms. Dryness is the key physical sign of having excess "*soda"*.

This dryness can be observed in the body organs like brain, skin, hair, nails and body mucous including the eyes, mouth and uterus. Another symptom of excess "*soda"* is the darkness of skin. Iranian traditional scholars believed that "*soda"* has cold temperament and this feature causes skin condensation which this increases the density of skin pigments and its darkness [5 - 7]. Symptoms similar to desperation and obsession show signs of *"soda"* dominance that affects the brain. Person with the "*soda"* dominance has no hope for the future and is permanently thinking of destruction and death.

In fact, most psychological symptoms of "*soda"* dominance can be compared with the symptoms of major depression in conventional medicine [6]. In order to treat "*soda"* dominance in ITM, the amount of "*soda"* in the patient's body should be reduced. To excrete the excess of "*soda"*, this humor should be first maturated for elimination using maturating drugs and subsequently purgative drugs should be consumed [2].

Several formulations (traditionally named *"Mozig-e-soda"*) have been introduced in ITM references for this purpose, one of which is a mixture of herbs including *Cordia mixa*, *Glycyrrhiza glabra*, *Adiantum cappilus-veneris*, *Foeniculum vulgare*, *Fumaria* spp, *Lavandula angustifolia*, *Echium amoenum*, *Melissa officinalis* and *Ziziphus jujuba*. After being powdered, the plants mixed together and then their aqueous extract is prepared using decoction method [8]. However, this form is not accepted by patients, especially in cases where medication must be taken for a long time.

Therefore, it is necessary to prepare suitable dosage form of the medicine. The aim of the present investigation was to prepare capsules of "*Monzig-e-soda*" as one of the most convenient dosage forms due to their easy consumption with no sense of unpleasant taste and then the stability of the dosage form was assessed.

MATERIALS AND METHODS:

Preparation of "*Mozig-e-soda*" Capsules: *Cordia mixa*, *Glycyrrhiza glabra*, *Adiantum cappilus-veneris*, *Foeniculum vulgare*, *Fumaria* spp, *Lavandula angustifolia*, *Echium amoenum*, *Melissa officinalis* and *Ziziphus jujube* **ration** were purchased from a local market in Tehran and identified by Dr. H. Hajimehdipoor. They were powdered and mixed in ratio of 2.4:1.5:1:1:1:1:1:1:2. They were extracted by using water as solvent (1:10), 90 °C, 2h.

The mixture was filtered and dried by using a spray dryer (Anhydro Co. Denmark). The capsules (size 0) were filled with the powder, 500 mg, and packaged in containers (30 capsules in each).

Stability Tests: Capsules were divided into two groups. To perform the stability testing, the first group was placed under accelerated Condition at 40°C and 75% humidity for 6 months. The second group (long term stability) was kept at 30°C for one year. Sampling was carried out at intervals of every two months [9]. Different tests were performed on the samples to determine the total phenolic compounds, the gum and mucilage as well as microbial levels.

Determination of Total Phenolics Content in the Product:

Preparation of Drug Sample: the contents of 10 capsules were mixed together. 500 mg of the powder was dissolved in 10 ml water and then was diluted to 25 ml with the same solvent.

Preparation of Pyrogallol Standard Solution: 5 mg of pyrogallol standard material was dissolved in 5 ml water and then diluted to 10 ml with the same solvent (0.5 mg/ml). Solutions with concentrations of 0.0625, 0.125 and 0.25 mg/ml were prepared respectively from the stock standard solution.

Methods: 2 ml of the drug sample/standard was transferred into the 25 ml flask and 1 ml of Folin-Ciocalteu reagent was added to the flask. Then 10 ml of distilled water was added and the solution was reached the volume using sodium carbonate (29% w/v). After 30 minutes, 1ml of the sample was transferred to the each well of 24 well-microplates. These steps were also conducted for the blank with the exception that instead of drug samples, distilled water was used. The absorbance of the samples and standards were measured at 760 nm using ELISA-reader [10 - 13].

The concentration of phenolic compounds in each sample was calculated according to the pyrogallol calibration curve.

Determination of Gum and Mucilage Content in the Product: The contents of 50 capsules were mixed with each other. Then 5 g of the herbal powder and 100 ml of distilled water were poured in an flask and placed in the refrigerator for 24 hours. After the desired time, the sample was filtered. 50 ml of the filtered liquid was mixed with 100 ml of alcohol (95%) and by filtering after 24 hours, gum and deposited mucilage on filter paper was weighted to determine their amount [14].

Microbial Tests: The herbal capsules were undergone microbial tests according to WHO guidelines [15].

RESULTS AND DISCUSSION: Maintaining a balance between the four humors of the body is very important. An imbalance in the body's four elemental humors such as the excess of black bile, causes associated symptoms. To overcome the problem, the excessive humor should be expelled from the body using maturating and purgative drugs [2]. Several formulations have been mentioned in ITM for this purpose which one of them including *Cordia mixa*, *Glycyrrhiza glabra*, *Adiantum cappilus-veneris*, *Foeniculum vulgare*, *Fumaria* spp, *Lavandula angustifolia*, *Echium amoenum*, *Melissa officinalis* and *Ziziphus jujuba* [8] was used in the present investigation.

The dried extract of the plants mixture was brown, sticky and fine powder with special odor which was prepared in hard gelatin capsules.

This dosage form is more acceptable than decoction for the patients. The stability of the capsules was assessed. Stability here means ensuring the sustainability of the identity, strength, quality and purity of the product. In fact, it can be interpreted that during definite time and under certain circumstances of storage, the product maintains its important and pre-approved characteristics.

Moreover, in order to estimate the half-life and expiration date and support the product label, the stability studies are necessary [9]. During the present study, the equation of $Y=2.8345X+0.0579$, $R^2 = 0.9992$ was obtained using pyrogallol calibration curve. The total phenolic compounds (expressed as pyrogallol equivalents) in "*Mozig-e-soda"* capsules at 30 °C and 40 °C and at different times has been shown in **Table 1**.

TABLE 1: CONTENTS OF PHENOLIC COMPOUNDS, GUM AND MUCILAGE IN "*MOZIG-E-SODA*" CAPSULES IN ACCELERATED AND LONG-TERM STABILITY TESTS

Time (month)	Phenolic compounds (%)		Gum and mucilage (%)	
	30 °C	**40 °C**	**30** °C	**40** °C
0	1.841±0.002		17.07±0.17	
2	1.838±0.010	1.824±0.006	16.94±0.38	16.97±0.55
4	1.826±0.044	1.812±0.004	16.65±0.15	16.67±0.42
6	1.815±0.011	1.808±0.012	16.77±0.31	16.83±0.67
8	1.810±0.024	-	16.77±0.67	-
10	1.792±0.036	-	16.53±0.20	-
12	1.788±0.013	-	16.60±0.69	-

Moreover, the diagrams of reduction percentage of components have been presented in **Fig. 1**. Microbial levels of capsules were in agreement with WHO acceptable limits [15].

Different studies have been conducted to determine the stability of herbal products. One of these studies evaluated the stability of *Rasayan churna* (an Indian herb). The stability studies has been conducted at the temperature of 40 °C ± 2 and relative humidity (RH) of 75% ± 5 and a temperature of 25 °C ± 2 and RH of 60% ± 5. Physicochemical parameters and microbial cultures were evaluated for 6 months, and long-term stability for 1 year. Sampling was conducted at time points of 0, 1, 3, 6 and 12 months. The results showed no changes in the color, smell and taste of the products under accelerated conditions within 6 months. In addition, long-term sustainability tests confirmed the stability of the drug in the year [16].

In another study performed on the stability of Black cohosh, polyphenolic compounds and triterpene glycosides of the plant were evaluated and the results showed no significant changes in the phytochemical constituents for three years.

However, the polyphenolic compounds in Black cohosh decomposed more rapidly and therefore had a lower stability and half-life compared to the other components [17].

In the present study that investigated the stability of "*Mozig-e-soda"* capsules, no changes in color, smell and taste of the drug powder in capsules was observed. Total phenolic contents of the products as well as gum and the mucilage of the herbal powder showed no significant changes within six months under accelerated conditions at 40 °C and 75% humidity. In fact, the level of changes in these plant components is less than 5% which indicates the stability of the drugs in adverse weather conditions and transportation [9]. Gum and mucilage as well as phenolics were decreased with the same rate as it can be seen in **Fig. 1**. Long-term tests also confirmed the stability of the drug at 30 °C for one year. Although the rate of decrease in phenolics is more than gum & mucilage (**Fig. 1**), the difference is negligible. Thereby, according to ICH [9] and using the equation Y = 2X, which X is the duration of long-term stability test, a two-year expiration date can be predicted for the drug. Although for determination of actual expiration date of a drug, tests should be performed for the entire anticipated duration on the product. Results of microbial tests on the products in both accelerated and long-term conditions are also confirmed the stability of the product. Therefore, it can be concluded that phenolic compounds present in the product, as well as gum and mucilage have low decomposition rate and can be considered as the main marker of quality control of "*Mozig-e-soda"* product.

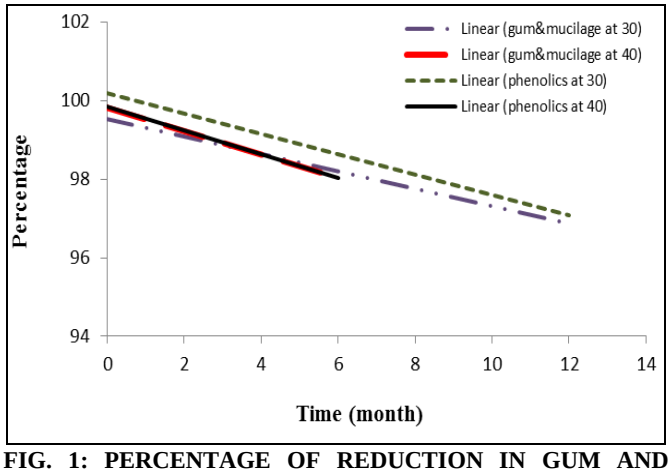

FIG. 1: PERCENTAGE OF REDUCTION IN GUM AND MUCILAGE AND PHENOLICS CONTENT OF "*MONZIG-E-SODA*" CAPSULES DURING ACCELERATE AND LONG TERM STABILITY TESTS

CONCLUSION: Due to the low variations of phenolic compounds, gum and mucilage in *"Mozig-e-soda"* capsules that has been prepared by spray-drying method, and based on the stability studies under accelerated conditions at 40 °C and 75% humidity as well as stability studies under normal condition (30 °C), it can be concluded that the *"Mozig-e-soda"* product is stable for at least two years.

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DECLARATION OF INTEREST: The authors declare that there is no conflict of interest.

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