



# A Comparative In-Vitro Study for Evaluation of Physicochemical Properties of the Domestic and Innovator Brands of Sertraline Hydrochloride Tablets Available in the Iranian Market

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## ABSTRACT

**Background:** The present study was aimed to assess the quality of Iranian and innovator sertraline hydrochloride (SER) tablets available in the Iranian market. This study could make it possible to provide adequate evidences confirming the similar physicochemical quality of Iranian and imported SER products and could subsequently decrease the therapy costs owing to the more affordable costs of Iranian medicines compared to the imported ones.

**Methods:** Seven products including one imported and six Iranian SER tablet brands were purchased from local pharmacy stores in Tabriz. Quantification of the amount of active ingredient in assay, uniformity of dosage units and dissolution tests were performed using an HPLC method recommended by USP monograph and other physicochemical properties were assessed in accordance with the USP general recommendations.

**Results:** According to the obtained results, the amount of active ingredient in all the products met the acceptable range (%90 - %110); the content of all the studied products was uniform ( $AV \leq 15$ ); and all the products passed the dissolution test at the first stage ( $Q_{30} \geq 85\%$ ); the average weight of all the products was uniform with RSD% of less than 5%; except for one product with friability of 15.8% (due to the coating issue), all products' hardness ( $\leq 10$  Kg) and friability ( $\leq 1\%$ ) were acceptable and all of them completely disintegrated after 30 min.

**Conclusion:** The results of this study illustrated the acceptable quality of the most Iranian brands of SER compared to the innovator brand regarding the studied physicochemical properties.

## Introduction

Nowadays, non-standard drugs are of serious clinical concerns treating public health. These drugs have some problems such as either excessive or low concentration of ingredients, contamination, low quality ingredients, incorrect packaging and low stability.<sup>1</sup>

Considering the inevitable position of the pharmaceutical industry in health system and the apparent effects of low-quality drugs on public health, no number of low-quality drugs is acceptable. Until recently, it had been thought that counterfeit drugs often contain ineffective and incorrect ingredients, but recent forensic studies has revealed that many of these products actually contain harmful substances, in which case not only the patient will deprive from the required treatment

but possibly suffer from side effects of these harmful substances, also.<sup>2</sup>

Non-standard drugs are the inevitable outcome of lack of good manufacturing practice and in pharmaceutical industry, especially in developing countries.<sup>2</sup> The numerous studies have indicated the different quality of diverse brands of a pharmaceutical formulation. In a study in Venezuela, for instance, primaquine tablets contained 19-168% active ingredient, which was out of the acceptable range;<sup>3</sup> in Ghana, one of the three available sulfadoxine-pyrimethamine products had poor solubility resulted in low bioavailability and efficacy;<sup>4</sup> and in a study conducted in Iran, although the quality of the majority of the studied carbamazepine, phenobarbital and phenytoin products were acceptable with respect to the

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Pharmacopoeial acceptance criteria, there were some products requiring formulation reconsiderations particularly regarding assay and content uniformity.<sup>5</sup> In contrary, there are some studies proving that despite the differences in price no significant efficacy and safety differences were spotted between innovator and generic brands.<sup>6,7</sup>

The present study was performed on SER, the drug with an IUPAC name of (1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine. It has an antidepressant effect through selective inhibition of serotonin reuptake and is utilized to cope with a number of mental disorders such as major depression, obsessive-compulsive disorder, body dysmorphic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, panic disorder and social anxiety disorder.<sup>8</sup>

Because of low costs of production and labour in Iran, a price gap usually exist between Iranian and imported medicines, which results in the formation of a misgiving in the general public regarding the lower quality of Iranian products. It is possible to turn the low prices on Iranian products compared to the innovator ones into an opportunity to decrease the imposed therapy costs on health system *via* convincing healthcare professionals and patients to rely on domestic pharmaceutical products. Post-marketing quality control studies done by authorized laboratories or academia could assess the quality of pharmaceutical products after entering the market and could provide adequate evidences showing the similar quality of marketed Iranian made and imported products regarding the physicochemical properties. Therefore, in order to somehow clarify the situation in the case of SER tablets, in the present work a post-marketing quality control study was carried out to evaluate the quality of different brands of SER tablets available in the Iranian market using physical tests (uniformity of weight, hardness, friability), chemical (assay) and performance (dissolution, content uniformity and disintegration) tests.

## Materials and Methods

### Chemicals and reagents

Working standard powder of SER with a purity of 100.12% was a gift from Zahravi Company (Tabriz, Iran), ortho-phosphoric acid, glacial acetic acid, acetonitrile and sodium acetate anhydrous were purchased from Merck (Darmstadt, Germany) and methanol was prepared from Scharlau (Barcelona, Spain).

Seven products of various manufacturers were purchased from local pharmacy stores in Tabriz, including one innovator (A) and six Iranian brands (B, C, D, E, F, G) each having a single batch number. All the products were scored film-coated tablets containing 100 mg SER. The expiration dates of the collected products were in the range of

02/2018 to 07/2020.

### Apparatus

Different instruments including analytical balance (A&D Weighing, San Jose, CA), hardness tester (Erweka, Germany), friability tester (Erweka, Germany), disintegration tester (Erweka, Germany), dissolution tester (Caleva, Germany), sonicator (Liarre, Italy), pH meter (Metrohm, Switzerland) and HPLC system equipped with a UV-Vis detector (Knuar, Germany) were used in present study.

In order to quantify the amount of active ingredient in assay, uniformity of dosage units and dissolution tests, an HPLC technique based on USP monograph on SER tablets was applied, where the separation was achieved using a mobile phase of methanol and 0.1% (v/v) phosphoric acid (50:50 v/v) with a pH value of 4.5 at a flow rate of 1.0 ml/min, with a L10 column (CN chemically bonded to porous silica) at 30 °C and UV detection at wavelength of 210 nm.<sup>9</sup>

### Suitability of the HPLC method for quantitative purposes

Prior to the quantitative analysis, the suitability of the mentioned HPLC method for the intended purpose was evaluated *via* calculating the partial method validation (linearity, accuracy and precision) and system suitability (capacity factor, theoretical plate numbers, tailing factor and repeatability of peak areas) parameters using the analysis of SER working standard solutions.<sup>10,11</sup>

The partial method validation was conducted with respect to the ICH Q2(R1) guidelines,<sup>10</sup> where 5 mg of SER standard powder was weighed accurately and dissolved in 100 ml of mobile phase to obtain a standard solution with a concentration of 50 µg/ml, which was diluted serially using the mobile phase to prepare working standard solutions with concentrations of 12.5, 18.75, 25, 37.5, 50 µg/ml. These working standard solutions were analyzed in triplicate using the mentioned HPLC method and the obtained average peak areas were plotted against the concentrations of studied solutions to achieve the calibration equation of the method, which was utilized to calculate the accuracy and precision of the method at the lower, middle and upper levels of the linearity range.

The system suitability parameters were calculated using the chromatogram obtained from the analysis of a standard solution with a concentration of 25 µg/ml, a concentration equal to that would be utilized in assay test.

The capacity factor was calculated using the Equation 1<sup>11</sup>, where  $k'$  is capacity factor,  $t_R$  is the retention time of the peak, and  $t_0$  is the dead time of the column.

$$k' = (t_R - t_0) \quad \text{Eq.(1)}$$

Theoretical plate numbers was calculated using the equation below<sup>11</sup>, where  $N$  symbolize theoretical

plate numbers,  $t$  is the retention time of the peak, and  $W$  is the peak width.

$$N = 16 (t/W)^2 \quad \text{Eq. (2)}$$

Equation 3<sup>12</sup> was utilized to calculate tailing factor, where  $T$ ,  $W_{0.05}$  and  $F$  are tailing factor, width of the peak at 5% of the height and the distance from the peak maximum to the leading edge of the peak at 5% of the height, respectively.

$$T = W_{0.05}/2F \quad \text{Eq. (3)}$$

Finally, in order to report the repeatability of the responses, RSD value among the peak areas obtained from the analysis of the standard sample in quintuplicate, was calculated.

### Assay Test

In order to prepare sample solution, at first a stock solution with a concentration of 500 µg/ml was prepared, where 20 tablets were powdered completely and the amount equivalent to 100 mg of SER transferred to a 200-ml volumetric flask, after that 100 ml of 0.1% phosphoric acid was added followed by the sonication for 15 min, then 80 ml of methanol was added to the flask and the mixture was sonicated for an additional 10 min and finally the mixture was cooled, filtered if necessary and diluted with methanol to the volume.<sup>9</sup> In the case of product G, the coating material made it difficult to powder the tablets completely; therefore, the sample preparation procedure was modified, where 10 intact tablets were transferred into the 1000 ml volumetric flask containing 500 ml of 0.1% phosphoric acid, the mixture sonicated for 15 min, then 400 ml of methanol was added into the mixture and sonicated for further 10 min and finally the cooled mixture was diluted to the volume using methanol.

From the sample stock solution, the working solution with a concentration of 25 µg/ml was prepared through diluting the stock solution using the mobile phase. A portion of the solution was passed through a 0.45 µm nylon filter and first few millilitres discarded and rest of the filtrate was collected as injectable samples into HPLC. Each sample was injected in triplicate (50 µL).

In order to calculate the assay amount, the below equation was applied:

$$\text{Amount}(mg) = 200 \text{ ml} \times 20 \times C \times r_t/r_s \quad \text{Eq. (4)}$$

Where 200 ml is the volume of the flask, 20 is the rate of dilution,  $C$  is standard solution's concentration,  $r_t$  is the peak area of sample solution and  $r_s$  is the peak area of standard solution with a concentration of 25 µg/ml.<sup>9</sup>

### Uniformity of Dosage Units

According to the USP recommendations,<sup>12</sup> uniformity of the dosage units test could be carried out in two ways: content uniformity and weight variation. In tablets, if the content of active ingredient is equal to or more than 25 mg or 25% of the total weight of the dosage unit, the weight

variation method should be used; otherwise the content uniformity would be the method of choice.

Since SER film coated tablets contain 100 mg of active ingredient, weight variation method was chosen to determine the uniformity of dosage units, where representative samples of 30 dosage units of each product with a single batch number were randomly selected and 10 tablets were chosen for the first step, where each one was accurately weighed, all the tablets were crashed and powdered and the amount of active ingredient in a weight equivalent to one tablet was determined using the HPLC method described in assay test. In the case of product G, in order to quantify the amount of active ingredient in a amount equivalent to one tablet, the method explained for the preparation of sample solution in assay test was applied. Then the amount of active ingredient in each tablet was calculated based on its weight.

Acceptance value for each 10 units, was calculated using the Equation 5:

$$AV = |M - \bar{X}| + ks \quad \text{Eq. (5)}$$

Where  $AV$  is acceptance value,  $\bar{X}$  is the average content of the dosage units,  $k$  is acceptance coefficient and  $s$  is the standard deviation. Because the  $T$  value for SER tablets was equal to 100 ( $T = (90 + 100)/2$ ) and less than 101.5, the value of  $M$  could be defined as:

- If  $\bar{X} < 98.5\% \rightarrow M = 95.8\%$
- If  $\bar{X} > 101.5\%, \rightarrow M = 101.5\%$
- If  $98.5 < \bar{X} < 101.5\% \rightarrow M = \bar{X}$

The value of  $k$  defined based on the number of dosage units ( $n$ ) as below:

- If  $n = 10 \rightarrow k = 2.4$
- If  $n = 30 \rightarrow k = 2.0$

### Dissolution Test

900 ml of acetate buffer, which was prepared through dissolving 1.627 g of sodium acetate anhydrous and 1.44 ml of glacial acetic acid in 900 ml water, was used as a dissolution medium. The pH of the prepared medium was adjusted to a pH value of 4.5 using glacial acetic acid. The USP apparatus 2 (rotating paddle) with a speed of 75 rpm was utilized for the test and the temperature of the medium was set at 37 °C during the test. Sampling was done at the end of 30-minute time period,<sup>9</sup> a portion of the solution collected at the end of the test, was passed through a 0.45 µm filter and diluted using the fresh medium to obtain a test solution with a final concentration of 28 µg/ml and finally the quantity of dissolved SER in samples ( $Q_{30}$ ) was determined using the HPLC method described in assay test.

In order to prepare a standard solution with a concentration of 28 µg/ml, 28 mg of standard SER powder was transferred into a 50 ml volumetric flask and dissolved in about 3 ml methanol, then 90.4 mg of sodium acetate anhydrous and 80 µl of glacial

acetic acid was added to the flask, consecutively and the mixture made up to the volume using water to obtain a stock solution with a concentration of 560 µg/ml, which was diluted using the dissolution medium to the concentration of interest.

For each product,  $Q_t$  was calculated as the percentage of the released drug at the end of 30 minutes.<sup>13</sup>

#### Friability Test

Since the average weight of SER tablets were in the range of 270 to 470 mg, twenty tablets were randomly chosen from each product to meet the USP requirements (the whole weight of as near as possible to 6.5 g). Tablets were carefully dusted off and accurately weighed. Then these tablets were transferred in the drum which was set at 25 rpm for 4 min. After 4 min, the test tablets were taken away from the tray, dusted off and weighed carefully to calculate friability percentage by using the below equation:<sup>14</sup>

$$\text{Friability \%} = ((A - B)/A) \times 100 \quad \text{Eq.(6)}$$

Where, A and B are the total weight of tablets before and after the test, respectively.

#### Tablet Hardness Test

Tablet hardness represents the mechanical stretch of tablets against breaking force and is defined as a force required to broken tablet dosage forms. In present study, 10 tablets were randomly chosen from each product and hardness of each tablet was tested by the hardness tester device<sup>15</sup> and the hardness was reported as the *mean required breaking force* ± *standard deviation*.

#### Disintegration Test

1000 ml of water was poured into each cell of the

disintegration apparatus, temperature was set at  $37 \pm 2$  °C and 6 tablets of each product were randomly chosen and put into each cell. After 30 minutes the cells were checked for total disintegration.<sup>16</sup>

#### Uniformity of Mass

In order to evaluate the uniformity of mass in coated tablets, twenty tablets were chosen randomly from each product and accurately weighed. The average weight and the relative standard deviation of the weights of examined tablets were calculated and reported. It should be declared that this test has been conducted in accordance with European Pharmacopeia instructions.<sup>17</sup>

#### Results and Discussion

The overall results obtained from the quality control of all the studied products in terms of assay, uniformity of dosage units, dissolution, disintegration, friability, hardness and uniformity of mass have been brought in Table 1.

In the following sections the results of each test were discussed in details.

#### HPLC system suitability results

The obtained chromatogram from the analysis of standard solution with a concentration of 25 µg/ml was shown in Figure 1. The system suitability parameters and partial method validation results depicted in Table 2, indicated the suitability of the applied HPLC method for the quantification of SER in a concentration range of 12.5 to 50 µg/ml, owing to the accuracy of 97.8 to 101.9%, precision of less than 2%, capacity factor of more than 1, tailing factor of less than 2% and repeatability of peak areas of less than 2%.

**Table 1.** The overall results obtained from the evaluation of physicochemical properties of all the studied brands of SER tablets.

Test	Brand Code							
	A	B	C	D	E	F	G	
Assay (%)	96.77 ± 0.51	102.44 ± 1.41	95.64 ± 1.86	96.24 ± 0.91	103.12 ± 1.23	90.21 ± 0.49	93.52 ± 1.19	
	2.95	4.33	7.33	4.44	4.59	9.46	4.6	
Uniformity of dosage units (AV)	1	95.48	96.02	90.06	89.95	88.48	99.06	94.75
	2	97.23	108.33	100.05	80.00	93.92	113.74	88.12
	3	93.88	100.67	111.88	99.13	92.15	107.24	90.38
	4	91.10	105.21	102.52	92.10	96.20	101.17	102.23
	5	99.58	87.32	99.09	97.10	100.86	105.88	91.04
	6	100.06	108.14	105.89	95.93	95.68	108.91	96.33
	$\bar{Q}\% \pm SD$	96.22 ± 3.44	100.95 ± 8.18	101.58 ± 7.31	92.20 ± 7.01	94.54 ± 4.17	105.99 ± 5.32	93.81 ± 5.1
Hardness (Kg ± SD)	8.5 ± 0.5	9.7 ± 0.7	6.0 ± 0.4	8.1 ± 0.4	6.7 ± 0.7	6.5 ± 0.6	7.9 ± 0.8	
Friability (%)	0.0000	0.0011	0.0037	0.0000	0.0017	0.0017	15.8005	
Disintegration ( $\frac{\text{Number of tested tablets}}{\text{Number of non-disintegrated tablets}}$ )	6	6	6	6	6	6	6	
	0	0	0	0	0	0	0	
Uniformity of mass	Weight	425.88	469	271.04	300.54	300.73	302.52	305.27
	RSD%	0.52	1.38	1.95	1.10	1.20	0.54	1.34

### Assay results

According to the SER tablets monograph for the assay test the tablets must contain 90.0%–110.0% of SER.<sup>9</sup> As it can be seen in Table 1, the amount of active ingredient in the innovator brand and all of the Iranian brands were in the acceptable range (varying from 90.2 to 102.4 %).

### Uniformity of dosage units

According to the interoperation criteria reported by USP, if the AV calculated for 10 tablets was equal or less than maximum allowed acceptance value ( $L1$ ), the product would be accepted at the first stage of test; otherwise 20 more tablets should be analyzed in the same way reported in stage one and the AV would be calculated for the total of 30 tablets; if obtained AV for the second stage was equal or less than  $L1$  and each unit contained active ingredient of more than  $[1-(L2 \times 0.01)]M$  and less than  $[1+(L2 \times 0.01)]M$ , the product would be accepted; or else it would be rejected, where  $L2$  is Maximum allowed range for deviation of each dosage unit from the calculated amount of  $M$ . According to the USP recommendations  $L1$  and  $L2$  are equal to 15 and 25, respectively, unless otherwise specified.<sup>12</sup>

Therefore, as it can be seen in Table 1, all products passed this test at first stage owing to the AV of less than  $L1$ .

### Dissolution

Dissolution test is done through the three stages

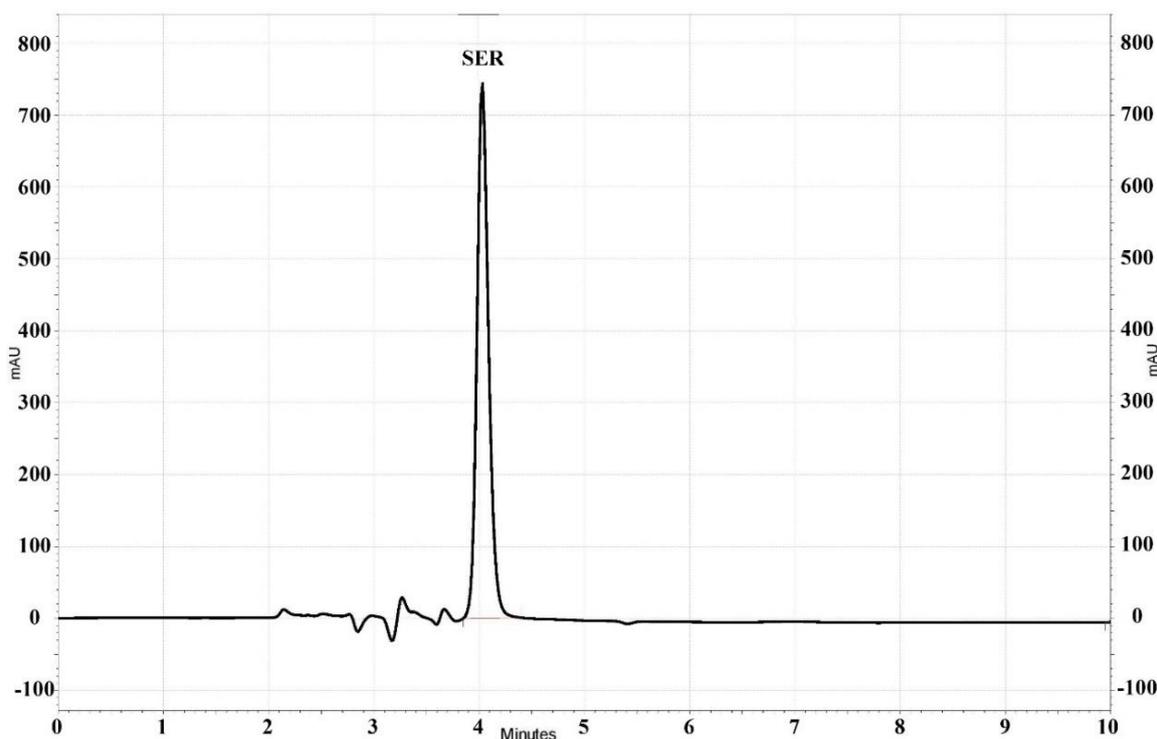
unless the results meet the criteria at either first or second stages.<sup>13</sup> The acceptance criteria for dissolution test of immediate release dosage forms are reported in the following:

- Accepted at first stage (S1): Sample number = 6 → Each unit is not less than  $Q_t + 5\%$ .
- Accepted at second stage (S2): Sample number = 6 → Average of 12 samples (S1+S2) is equal to or more than  $Q_t$ , no unit is less than  $Q_t - 15\%$ .
- Accepted at third stage (S3): Sample number = 12 → Average of 24 samples (S1+S2+S3) is equal to or more than  $Q_t$ , no more than 2 units are less than  $Q_t - 15\%$  and no unit is less than  $Q_t - 25\%$ .

Since, the  $Q_{30}$  stated in SER monograph is equal to %80, all the products were accepted at the first stage as a result of  $Q$  of more than 85%.

### Friability

According to the USP recommendations, the acceptable friability percentage for tablet dosage forms is less than 1%.<sup>14</sup> However in the case of film coated tablets, this test is not mandatory assuming that their friability should be less than acceptable allowed amount. As shown in Table 1, almost all the products had the friability of less than 0.004% as expected for film coated tablets.



**Figure 1.** The chromatogram obtained from the analysis of a standard solution of SER with a concentration of 25  $\mu\text{g/ml}$ . The separation was achieved using a mobile phase of methanol and 0.1% (v/v) phosphoric acid (50:50 v/v) with a pH of 4.5 at a flow rate of 1.0 ml/min, with a L10 column at 30 °C and UV detection at wavelength of 210 nm.

**Table 2.** The system suitability and partial method validation results.

Linear range ( $\mu\text{g/ml}$ )	Calibration equation	Regression coefficient	Accuracy (%) <sup>*</sup>	Precision (RSD%) <sup>*</sup>	Capacity factor ( $k'$ ) <sup>**</sup>	Repeatability of peak area (RSD%) <sup>**</sup>	Theoretical plate numbers ( $N$ ) <sup>**</sup>	Tailing factor ( $T$ %) <sup>**</sup>
12.5 – 50	$Y = 10723X + 35937$	0.996	90.7 – 101.9	0.1 – 1.7	1.1	1.6	1136	1.1

<sup>\*</sup>The accuracy and precision (repeatability) were evaluated at the lower (12.5  $\mu\text{g/ml}$ ), middle (25  $\mu\text{g/ml}$ ) and upper (50  $\mu\text{g/ml}$ ) levels of linear range.

<sup>\*\*</sup>The system suitability parameters were calculated based on the chromatograms obtained from the analysis of a working standard solution with a concentration of 25  $\mu\text{g/ml}$ .

Nevertheless in the case of product G, the obtained friability was 15.8%, much more than the acceptable allowed amount. Moreover, a coating issue was observed in assay and uniformity of dosage units tests of product G, where the coating material was separated as a paper-like layer during the tablet crushing (Figure 2), which interfered with the sample solution preparation procedure. Therefore, it can be concluded that the observed friability issue was raised due to the inadequate coating or application of unsuitable coating materials. Since the higher friability would affect the product's integrity during handling, storage and shipping either in company or in the pharmacy store, it could be suggested that the coating process of product G should be reconsidered to be able to improve the situation.



**Figure 2.** The paper-like coating material separated during the crushing of product G tablets.

### Hardness

Hardness of tablet dosage forms depends on different factors such as shape, compressing pressure and employed excipients in the formulation; it could also increase during the normal storage. The acceptable hardness for oral tablets is considered as a force of 4 to 10 Kg (39.2 to 98 Newton) required for breaking a tablet.<sup>15</sup>

As depicted in Table 1, all the products had acceptable hardness.

### Disintegration

According to the USP recommendations, in the case of immediate release coated tablets, if all the studied tablets are completely disintegrated at the end of the time period of 30 min, the product will pass the test.<sup>16</sup>

A short glance at the Table 1, indicates the acceptable disintegration of all the studied products.

### Uniformity of Mass

According to the European Pharmacopeia,<sup>17</sup> the acceptance criteria for uniformity of mass of coated tablets are reported in the following:

- If the average weight of 20 dosage units is less than 80 mg, the acceptable deviation from the mean is 10%.
- If the average weight of 20 dosage units is between 80 and 250 mg, the acceptable deviation from the mean is 7.5%.
- If the average weight of 20 dosage units is more than 250 mg, the acceptable deviation from the mean is 5%.

As it can be seen in Table 1, regardless of the differences among the average weights of different products, the relative standard deviation from the average weight for each product was less than 5%. Therefore, all the products represented the acceptable uniformity of mass.

### Conclusion

Almost all the SER brands available in the Iranian market had a desirable quality except for one of the Iranian brands, product G; it had a major coating issue resulting in difficulty in crushing the tablets to a completely powdered form required for the assay and uniformity of dosage units tests. Moreover, this product had a high friability percentage due to the same coating problem in spite of the fact that in the coated tablets the friability test is not mandatory assuming they are not susceptible to friability. Therefore, it can be said that the product G needs reconsiderations in its coating process to improve its quality, because the more friable the tablets, the more difficult to keep integrity during handling, packaging and shipping processes.

Regarding product F, it barely passed the assay test ( $90.2 \pm 0.48\%$ ), while the obtained  $Q$  for dissolution test was 105.9%. The observed disparity could be the result of poor uniformity of the content of tablets in the studied batch ( $AV$  of 9.46). Consequently, although product F passed all the individual tests, the inconsistency between the obtained results from assay and dissolution tests could point out to the necessity of minor changes in its formulation to improve the within batch consistency of the product.

It is worth mentioning that since the cis-(1S,4S) enantiomer of SER represents the therapeutic effects, one of the most important quality aspects of SER formulations is enantiomeric purity. Therefore, since the majority of the studied products had the acceptable physicochemical quality, it is suggested to conduct a further study on the enantiomeric purity of SER tablets available in the Iranian market to provide complimentary evidences confirming the comparable quality and efficacy of innovator and Iranian brands.

In sum up, it should be said that despite the necessity of in process and final product quality control in Iranian pharmaceutical industry, there are some Iranian brands still suffering from some issues in their formulations resulting in lower quality and consequently lower efficacy and probable impaired safety. Therefore, it can be concluded that the quality control of pharmaceutical products in industry should be carried out more precisely. Furthermore, it seems that conducting more post marketing surveillances in our country, especially in academia, could help regulatory bodies to be aware of the presence of low-quality products in Iranian pharmaceutical market and convince them to do stricter inspections leading to production of high quality domestic products.

#### Conflict of interests

The authors claim that there is no conflict of interest.

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