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Comparison of some physical parameters of different brands of acyclovir tablets marketed in Iran

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Abstract:

Acyclovir is the nucleoside analogue of guanosine, which is used as an antiviral drug. Since the quality requirements set for a higher quality product are necessary, the purpose of this study was to investigate the quality control characteristics of selected Iranian brands of acyclovir 400 mg tablets. Different brands and batches of acyclovir tablets were collected and subjected to various quality control tests such as weight variation, friability, hardness, disintegration and dissolution. The results obtained for all the selected brands of acyclovir were in acceptable range and, it can be stated that all brands of acyclovir tablets met the specification in quality tests.

Keywords: Acyclovir; Quality control; Physico-chemical properties

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1. Introduction

Acyclovir, (2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one), (figure 1) is the nucleoside analogue of guanosine, which is used as an antiviral drug. This compound exerts its antiviral effect by inhibiting viral DNA synthesis and is active against herpes viruses such as *Herpes simplex* virus (HSV), *Varicella zoster* virus (VZV), and *Epstein–Barr* virus (EB) (1).

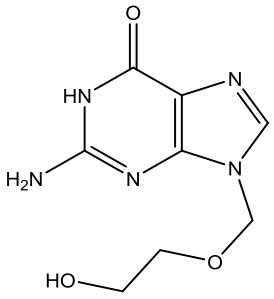

Figure 1. Chemical structure of acyclovir.

Acyclovir has poor solubility in water and is quickly eliminated from the body. The reported half-life of acyclovir is about 3 hours, and its bioavailability is not sufficient (2). Acyclovir is available in different dosage forms such as tablets, injection, ointment, and cream in the drug market in Iran. Currently, more than ten Iranian pharmaceutical company produced acyclovir dosage forms (3).

To supply patients with safe and appropriate products, the quality of manufactured products must be analyzed. Formulation properties, and manufacturing methods have essential role in the safety and efficacy of pharmaceutical products (4).

Due to patient convenience, suitable stability, and ease of administration, handling, and storage, tablets are the most common dosage forms (5). Tablet production is a multistep procedure that must be carried out in accordance with official regulations and guidelines. For the evaluation of tablets' quality, different pharmacopoeias such as U.S. Pharmacopeia (USP), British Pharmacopeia (BP), and/or the European

Pharmacopeia (EP) established some tests such as disintegration time test, dissolution test, uniformity of dosage units and assay test. However, non-pharmacopeia tests are also used (6,7).
This study aimed to evaluate and compare different brands and batches of acyclovir tablets available in the Iran market by some general pharmacopeia and non-pharmacopeia quality control tests.

2. Materials and Methods

2.1. Materials

Four Different Iranian Acyclovir tablet brands (400 mg) were purchased randomly from local pharmacies in Tehran, Iran in 2018-2019. Purchased tablets were checked for batch numbers, production, and expiration dates. The physico-chemical properties and pharmaceutical quality of tablets were evaluated according to USP39/NF34, 2016, and non-pharmacopeia tests. All tests were completed before the product's expiration date. HCl, NaOH and acetic acid were purchased from Merck (Darmstadt, Germany). Water was HPLC grade and all other reagents were analytical grades.

2.2. Visual Inspection

The shape and color of all tablets were visually examined and inspected for the presence of spots, chipping, cracking, and capping.

2.3. Length and thickness

The thickness and length of ten tablets of each brand were recorded by vernier caliper in millimeters (mm) and reported as mean ± standard deviation (SD).

2.4. Friability test

Friability was determined on 10 tablets. The samples were first de-dusted and weighed accurately and placed in the drum of the friabilator (Erweka TA GmbH, Germany). After 100 rotations (4 min at 25 rpm) the tablets were taken out. The tablets were weighed again after any residual dust from the tablets was removed. The friability is expressed as the percentage of weight loss. The percentage of weight loss is obtained according to the following equation (8,9):

Friability % = (Initial weight- Final weight) × 100 / Initial weight (Equation 1)

2.5. Hardness test

Ten tablets were taken randomly and diametric crushing strength was determined as Newton by a hardness tester (Erweka TBH -28, Germany). Data represented as mean ± SD (10).

2.6. Weight variation test

Twenty tablets of each brand were randomly selected and weighed individually by analytical balance. The percentage deviation of each tablet from the mean was evaluated according to the following equation (11):

Weight variation = (individual weight – mean weight) × 100 / mean weight (Equation 2)

2.7. Assay

The assay test was performed according to the United States Pharmacopoeia (USP 39) method (12).
Briefly, for preparing sample solution ten tablets of each brand were selected and powdered finely. An equivalent amount of 10 mg acyclovir transferred to 100 mL flask and dissolved in sodium hydroxide (0.1 N) and diluted with water to volume and filtered. Standard solution of acyclovir with concentration of 0.1 mg/mL was prepared by transferring 10 mg of standard powder of acyclovir to 100 mL volumetric flask, dissolving in NaOH (0.1 N) and diluting with water. 20 µL of each sample were injected into the HPLC/UV system mentioned in pharmacopeia assay method.
The equation 3 was used to calculate the percentage of the labeled amount of acyclovir.

% of the labeled amount of acyclovir = $(r_u/r_s) \times (C_s/C_u) \times 100$ (Equation 3)

r_u = Peak response from the Sample solution
r_s = Peak response from the Standard solution
C_s = Concentration of acyclovir reference standard in the Standard solution (mg/mL)
C_u = Concentration of acyclovir in the Sample solution (mg/mL)

2.8. Uniformity of dosage units

Weight variation method was used to obtain the uniformity of dosage units according to USP 39 monograph of acyclovir (12).
Briefly, for each brand at first stage ten tablets were selected and the percentage of acyclovir was calculated for each tablet. The acceptance value (AV) was calculated according to following formula (Equations 4-6):

$T \leq 101.5 \rightarrow$ IF $98.5\% \leq \bar{X} \leq 101.5\%$
then AV=KS (Equation 4)

$T \leq 101.5 \rightarrow$ IF $\bar{X} < 98.5\%$
then $AV = 98.5 - \bar{X} + KS$ (Equation 5)

$T \leq 101.5 \rightarrow$ IF $\bar{X} > 101.5\%$
then $AV = \bar{X} - 101.5 + KS$ (Equation 6)

T: Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. Unless otherwise stated, T is 100.0%.
$\bar{X}$: Mean of individual contents expressed as a percentage of the label claim
K: If n = 10, then K = 2.4
n: Sample size (number of units in a sample)
S: Sample standard deviation

2.9. Disintegration test

Disintegration time of tablets was determined by placing six tablets of each brand in the tubes in the basket of the disintegration apparatus (Erweka ZT6-1-D, Germany). Small metal discs were used to enable the immersion of the tablet completely. The basket was suspended in the one-liter beaker containing 900 mL water as a medium at 37±2°C. The disintegration time was taken to be the time at which no particle remained on the bottom mesh of the tube. Mean disintegration time was calculated for each of the brands and reported as mean ± SD (13).

2.10. Dissolution

Dissolution was tested according to USP using an apparatus type II (paddle method, Erweka DT 6R). Six tablets of each product were tested. In the dissolution apparatus, one tablet was placed in each vessel containing 900 mL 0.1 N HCl as the dissolution medium and paddle stirred at 50 rpm. The temperature was adjusted at 37 ± 0.5 °C. After 45 min, manually aliquot sample was taken and the absorbance of the samples was measured by UV spectrophotometry at 254 nm (12,14).

3. Results and Discussion

Four local brands were obtained randomly and coded as A, B, C, and D. The different batches of each brand were defined with Arabic numerals. The details of all taken marketed acyclovir tablets were shown in table 1. The brand A and C acyclovir tablets were packed in a light-resistant amber-colored blister while the brands B and D were packed in a clear blister. The physical appearance of all tablets used in this study was acceptable. The color of all tablets was white with a smooth texture and no defects (capping, cracking, and chipping) on the tablets were detected.
All studied brands were scored round in shape except brand D which was non-scored oval. The average length of round shape tablets was 12.5 mm and for oval shape tablets was 16.5 mm. The thickness of the tablets was between 3.78-5.90 mm.
The results of the friability test, hardness, disintegration time, weight variation, and dissolution were reported in table 2.
Friability test checks the tendency of the tablet to crumble, chip, or break upon abrasion or compression. The loss in weight indicates the ability of the tablets to withstand the wear. Loss of 1% tablet mass without any chipping or crashing is acceptable during the process. The results of friability tests were in the range of 0.02-0.99 %. According to obtained results, brand C had the lowest friability. The friability of all brands was less than 1% and passed the test.
Hardness expressed the strength of the tablet to resist the pressure. There is no reported requirement for hardness in pharmacopoeias. The suitable range of hardness for the oral tablet was reported between 4-10 kg or 39-98 newton (N) (11). The average hardness of all studied tablets was in the range of 78-192 N. Therefore, these products were strong enough to resist the stress of handling and packing.

Table 1. Details of collected acyclovir tablets 400 mg from local pharmacies.

No.	Code	Batch No.	Exp Date	Shape	Length (mm) Mean ± SD	Thickness (mm) Mean ± SD
1	A1	42	01-2019	Scored Round shape with flat faced	13.20 ± 0.06	3.79 ± 0.04
2	A2	44	02-2019	Scored Round shape with flat faced	13.10 ± 0.01	3.82 ± 0.03
3	A3	46	04-2019	Scored Round shape with flat faced	13.08 ± 0.03	3.79 ± 0.05
4	B1	V2	05-2022	Scored Round shape with flat bevelled edge	12.09 ± 0.06	3.90 ± 0.11
5	C1	7	09-2019	Scored Round convex shape	11.69 ± 0.02	4.78 ± 0.32
6	C2	10	02-2020	Scored Round convex shape	11.74 ± 0.02	4.83 ± 0.34
7	D1	131	01-2019	Non-scored Oval shape	18.37 ± 0.06	4.05 ± 0.10
8	D2	132	02-2019	Non-scored Oval shape	18.38 ± 0.04	3.94 ± 0.10
9	D3	135	05-2019	Non-scored Oval shape	14.52 ± 0.04	5.91 ± 0.70

Table 2. The results of pharmacopeia and non-pharmacopeia tests for acyclovir 400 mg tablets collected from local pharmacies.

No.	Code	Weight (mg) Mean ± SD	Friability (%)	Hardness (N) Mean ± SD	Disintegration time (min)	Dissolution (%) Mean ± SD	Assay (%)	Uniformity of dosage units (AV)
1	A1	651 ± 0.01	0.31	151 ± 15	5.27 ± 0.36	87 ± 4	102.3	5.51
2	A2	655 ± 0.01	0.44	148 ± 12	3.42 ± 0.35	89 ± 6	102.1	3.09
3	A3	644 ± 0.01	0.25	192 ± 24	4.69 ± 1.38	88 ± 4	101.9	3.06
4	B1	522 ± 0.01	0.99	94 ± 19	7.33 ± 0.52	93 ± 12	99.1	2.77
5	C1	539 ± 0.01	0.09	165 ± 26	10.23 ± 1.42	91 ± 9	100.1	3.93
6	C2	547 ± 0.01	0.02	78 ± 13	8.28 ± 1.05	91 ± 4	100.2	3.02
7	D1	574 ± 0.02	0.09	163 ± 9	2.90 ± 0.00	95 ± 7	101.1	7.29
8	D2	559 ± 0.03	0.48	131 ± 14	0.77 ± 0.00	102 ± 14	100.4	14.05
9	D3	558 ± 0.03	0.07	166 ± 45	1.12 ± 0.13	94 ± 6	100.4	13.77

Weight variation of tablets can represent the uniformity of active ingredients in dosage units. If the variation is out of the specification, the tablets are thought to contain less or more active ingredient and resulting in an ineffective therapeutic response. However, weights within each brand show uniformity, there were weight variations between the studied brands. The mean weight of acyclovir tablets was about 550 mg for brands B-D and 650 mg for brand A. The weight variation for all the brands was acceptable and none of them deviate from the specified limit.

Assay test is one of the important pharmacopeia tests which is demonstrated the amount of drug substance in each dosage form is therapeutically adequate. According to the USP monograph of acyclovir tablet, the acceptable range for assay test is 90.0% - 110.0%. Based on the obtained results (Table 2), the assay of the tested tablets was between 99.1% - 102.3% which was in acceptable range.

Uniformity of dosage unites test guarantee the consumer which each dosage form has the similar amount of active pharmaceutical ingredients. The maximum allowed amount of AV in this test was 15 in case of n = 10. If the result did not meet the requirement the test should be repeated with another 20 dosage forms. According to obtained results the amount of AV for tested tablets were between 2.77 - 14.05.

The disintegration time was used to ensure that the drug substance is fully available for dissolution in the gastrointestinal tract. According to the USP, immediate release film coated tablets should disintegrate completely in less than 30 minutes (15). The results of the disintegration test for the tablet were in the range of 46 sec to 10 min. Based on obtained disintegration time, all the tablets used in this study completely disintegrate in less than 30 min and complies with the limit of pharmacopeia.

Dissolution is the process that which the active ingredient of dosage forms enters into a solvent to yield a solution. Through the small intestinal walls, the dissolved active ingredient enters the bloodstream. The blood carries the active ingredient to the site of therapeutic effect to produce the desired therapeutic outcome.

The dissolution test is an important tool for quality control and ensures the therapeutic effectiveness of dosage forms and their bioavailability. Generally, the sampling time and the acceptance limit of the dissolution test are mentioned in the USP monograph of drugs. According to the acyclovir tablet monograph, 80 % of the labeled claim of acyclovir tablet should dissolve in 45 minutes. All studied brands released between 87-102% and meet the US pharmacopeia requirement (12, 14).

4. Conclusion

This study was performed to compare the physical quality of marketed acyclovir tablets in Iran. Selected acyclovir tablets were analyzed by standard methods and apparatus. According to the obtained results, it could be concluded that the studied tablets of acyclovir 400 mg met the quality control requirements of mentioned tests. It is necessary to take further steps and additional procedures to ensure product quality and safety.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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