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Research Article

IN–VITRO PHARMACEUTICAL EVALUATION OF TWO BRANDS OF DISPERSIBLE ACETYL SALICYLIC ACID TABLETS AVAILABLE IN OMAN

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ABSTRACT

Acetyl salicylic acid (ASA), a non-steroidal anti-inflammatory drug (NSAID) is widely used for its analgesic, antipyretic, anti-inflammatory and anti-thrombotic action. The aim of the present study was to investigate the pharmaceutical equivalence of two brands of dispersible ASA tablets marketed in Oman. Two different brands of dispersible ASA tablets (300mg) were purchased from the retail pharmacy outlets and their pharmaceutical quality were assessed by using *in-vitro* tests as per the British Pharmacopoeia (BP) and unofficial standards as recommended by the manufacturers**.** The assessment of tablets included the evaluation of uniformity of weight and diameter, friability, crushing strength, disintegration and chemical assay by volumetric titration and colorimetric methods to determine the content of active pharmaceutical ingredient (API). Both brands of the ASA tablets passed the BP standards for uniformity of weight and diameter, disintegration, friability and crushing strength. However one of the two brands did not comply with the standard assay of content of active ingredient. Thus based on these results it can be concluded that these two brands of ASA are not pharmaceutically equivalent.

Key words: ASA tablets, pharmaceutical equivalence, disintegration, volumetric method.

INTRODUCTION

Acetyl Salicylic Acid (ASA) or Aspirin (Figure 1) is one of the oldest and the most commonly used Non steroidal anti-inflammatory drug (NSAID). It is an effective analgesic, anti-inflammatory, anti-thrombotic and antipyretic agent, that primarily acts by permanently inactivating the cyclooxygenase (COX)-mediated activities of prostaglandins through irreversible binding unlike other NSAIDs, which are reversible inhibitors (Gordon *et al*., 1994; Patrono *et al*., 2001). ASA is rapidly and extensively absorbed by first-order kinetics and distributed throughout the body fluids. Following oral administration, it is rapidly metabolized and excreted as salicylate (Rhaman *et al*., 1991).

ASA is one of the safest, least expensive NSAID with multinational brands available on the market place. The various brands available in the market are considered pharmaceutically equivalent if they contain the same amount of active ingredient in the identical dosage form and meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity), but may differ in characteristics such as shape, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling requirements etc. [FDA CDER, 2004].

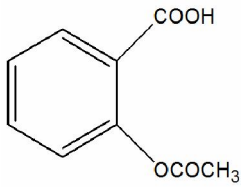

Figure 1. Structure of Acetyl Salicylic Acid.

It is the joint responsibility of the manufacturers and the drug law enforcing agencies to ensure that various marketed pharmaceutical products containing the same active ingredient in the identical dosage forms are uniform, safe and effective. The safety and efficacy of drug products can be guaranteed when their quality is reliable and reproducible

from batch to batch. To ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product (Chow, 1997).

Pharmaceutical equivalent products help the practitioners and pharmacists in substitution of one brand for the other in case of non availability; however this substitution is quite controversial and is often met with suspicion among patients and physicians (Meredith, 2003).

ASA is one of the most commonly used NSAID in clinical practice, therefore, it is necessary to monitor and ascertain the quality of the various brands available in the market. The quality i.e. safety and efficacy of solid dosage form such as tablets can readily and satisfactorily be assessed by carrying out *in- vitro* Pharmaceutical tests. The present study was carried out to evaluate the pharmaceutical equivalence of two brands of dispersible ASA tablets available in Oman using *in vitro* methods as per the British Pharmacopoeia (BP) and unofficial standards as recommended by the manufacturers**.** The assessment of tablets included the evaluation of uniformity of weight and diameter, friability, crushing strength, disintegration and chemical assay by volumetric (visual titration) and colorimetric methods to determine the content of active pharmaceutical ingredient (API).

MATERIALS AND METHODS

Two different brands of dispersible ASA 300 mg tablets were purchased from the retail pharmacy and were coded as A and B. The labeled shelf life was three years from the date of manufacturing and the tablets were evaluated one year before the labeled expiry date.

Equipments

Hardness tester Monsanto type (Bellstone Hi–Tech International): Friabilator (Bellstone Hi–Tech International); Micrometer screw gauge; Digital balance (Sartorius); Digital tablet disintegration test apparatus (Bellstone Hi–Tech International); Colorimeter (Spectronic 20D+, Thermo Electron corporation)

Chemicals

Conc. Hydrochloric acid; 0.1M, 0.5M and 1M NaOH; Potassium chloride; 0.025 M Ferric chloride; 0.5 N Hydrochloric acid and Phenol red indicator.

Methods

Identity, uniformity of weight and diameter, friability, crushing strength, disintegration and assay for the content of active ingredients by titrimetry (British Pharmacopoeia, 2009) and colorimetry (Abdulkadir *et al.,* 2009) were done as described in the British Pharmacopoeia and literature. All the assays were carried out in triplicate.

Data analysis

Data for hardness, friability, diameter, weight uniformity test, disintegration and content uniformity of the tablets were analyzed by determining the mean ± standard deviation. Student's *t* test was used for determining significance. P values <0.05 were considered as significant.

Hardness

Hardness of the tablet was measured using Monsanto hardness tester. Ten tablets of each brand were randomly selected and the hardness of the tablets was determined (n=10).

Friability

Ten randomly selected tablets for each brand were initially weighed and placed in a friabilator chamber. The friabilator was operated at 25 rpm for 4 minutes (up to 100 revolutions). Thereafter, tablets were removed, dusted and reweighed. The percent (%) friability was then calculated by using following formula (Kalakuntla *et al.*, 2010). The test was repeated three times for each brand of ASA tablets.

$$\% \text{ Friability} = \frac{WBT - WAT}{WBT} \times 100$$

WBT : Weight Before TestWAT : Weight After Test

Diameter

Random samples of 10 tablets were selected from each brand and their diameter was calculated in centimeters with the help of micrometer screw gauge.

Weight variation

The weights of twenty tablets were determined individually using an electronic digital balance. The average tablet weight and standard deviation were calculated and compared with the permissible limits.

Disintegration

A 900mL beaker was filled with distilled water and was maintained at 37±0.5°C. Six tablets of each brand were selected and placed in each of the cylindrical tubes of the basket and connected to the disintegration apparatus. To avoid the floating of tablets while tube move upwards and downwards in water, discs were used. The time taken to break each tablet into small particles and pass out through the mesh at the bottom of the tube was recorded. Mean disintegration time was calculated for each of the brands.

Content uniformity

Acid- Base titration method: twenty tablets of each brand of ASA were weighed and crushed to powder. To a weighed quantity of tablet powder equivalent to 500mg of ASA, 30mL of 0.5M of Sodium hydroxide was added. The solution was boiled for 10min and titrated with 0.5M hydrochloric acid using phenol red as an indicator till the color changed from red to yellow. A blank titration was also performed by omitting the sample. The difference between the two titrations was used to determine the percentage content of ASA in the tablets. Each 1mL of 0.5M sodium hydroxide is equivalent to 45.04mg of ASA.

Colorimetric analysis: A series of working solutions with different ASA concentrations were prepared and complexed with Ferric chloride solution. The absorbance of each solution was measured at 530nm and a calibration curve was constructed. Using the standard curve, the amount of ASA in each brand was determined.

Standard solution of ASA

A stock standard solution (800µg/mL) was prepared by dissolving 80 mg of ASA powder in 10mL of 1M NaOH. The solution was boiled, cooled and diluted to 100mL with purified water. Working standards for constructing a calibration curve were prepared by pipetting 10, 8, 6, 4 and 2mL aliquots of the stock standard solution into separate 100mL volumetric flasks and diluting to volume with 0.025M $FeCl_3$.

Sample preparation

Three ASA tablets from each brand were weighed individually and powdered. Each powdered tablet was quantitatively transferred to 250mL volumetric flask and 10mL of 1M NaOH was added to it. Solutions were heated to boiling, cooled to room temperature and were diluted up to the mark with purified water. 5mL aliquots of each sample were pipetted into separate 100mL volumetric flasks and each flask was diluted to volume with 0.025M ferric chloride solution. Absorbance of standard solutions and unknown was measured at 530nm by using 0.025M $FeCl_3$ as blank.

RESULTS AND DISCUSSION

The results of various quality control tests performed on two different brands of ASA tablets are presented in table I and table III. In order to determine the ASA content in tablets by $FeCl_3$-colorimetric method, five working standard solutions were prepared and their absorbance was measured to construct standard calibration curve. A liner regression of the standard absorbance data of working solutions (Table II) in statistical software, SPSS gave the following equation which was used to determine the ASA content of analyzed tablets.

$Y = 11.155x+0.0096 \quad (R^2 = 0.9912)$

Hardness of ASA tablets was found to be in the range of 4.5 to 6Kg/cm² indicating good mechanical strength. The hardness values of both the brands met the pharmacopoeial requirement and based on the results it could be expected that tablets would be resistance to capping or breakage while handling during transportation and storage. However, a significant difference was observed in the mean crushing strength of the two brands by student's *t* test.

Weight loss due to friability in both marketed preparations was found to be less than 1% indicating that both brands are mechanically stable and will not undergo any

Table I. Results of official and unofficial quality control tests on two brands of Aspirin tablets

Brand	Hardness (Kg/cm^2) Mean±SD, (n = 6)	Friability (%) (n = 10)	Diameter (cm) Mean±SD (n=10)	Weight Uniformity (mg) Mean±SD (n=20)	Disintegration time (sec) Mean±SD (n = 6)
A	6±0.1	0.63	0.806±0.015	364.41±2.29	32.3±3.01
B	4.55±0.37	0.65	0.865±0.013	397.91±2.06	32.6±2.8
p-value (Student's *t* test)	<0.05	0.07	<0.05	<0.05	0.846

Table II. Standard Absorbance values of ASA for plotting standard curve by colorimeter

Absorbance	Stock concentration (mg/mL)	Stock number
0.177	0.0159	1
0.357	0.0318	2
0.554	0.0477	3
0.758	0.0637	4
0.865	0.0796	5

Table III. Content uniformity assay of ASA in two brands by acid- base titration and colorimetric method

Remarks as per the BP permissible limit (95-105%)		% ASA content		Content found (mg) Mean±SD		Brand
Colorimeter	Titration	Colorimeter	Titration	Colorimeter	Titration	
Failed	Failed	92.2	93.57	276.6±2.14	280.7±4.4	**A**
Passed	Passed	100	97.57	300±5	292.7±0.6	**B**
				0.335	0.287	p-value (Student's *t* test)

wear or tear during transportation. Brand B showed more % weight loss (0.65%) than brand A (0.63%). However, both the brands met the Pharmacopoeial requirement and no significant statistical difference was found in the mean friability.

Diameter of two brands of ASA tablets was well within the permissible limits (average±5%) and thus met manufacturer's requirements for tablet diameter. Result suggests that they are uniform in size and shape. Comparison of values for both brands showed no difference in diameter as mean diameter of brand A and B was found to be 0.806cm and 0.865cm respectively. Variance of two brands was also found to be similar.

Weight uniformity test for tablets is required to ensure that the drug content in each tablet is distributed in a narrow range around the label strength because slight variation in weight of tablet reflects variation in the content of active ingredient. According to the BP, drug products whose strength is >250mg, permissible limit of ±5% of the average is required to pass the test for weight uniformity. Both the commercial products possessed acceptable uniformity of weight as per the pharmacopoeial limit. 20 randomly selected

tablets in brand A and B were within the mean±5% B.P range for weight uniformity, (337.1-391.7) mg and (368.1-427.7) mg respectively. P- value for weight uniformity was found to be statistically significant (<0.05).

Disintegration evaluates availability of a drug for dissolution and absorption from the Gastrointestinal tract. The results presented in table 1 reveals rapid disintegration of both the products. Fast disintegration is required for analgesics in order to get prompt relief. Both the products meet the disintegration limit set by the British Pharmacopoeia. According to the BP 2004, the time limit for disintegration of dispersible tablets is <3 min. Statistical analysis showed no significant difference in mean disintegration time of two brands.

Both the brands were assayed for the acetyl salicylic acid content by acid base titration and colorimetry to study and compare the efficacy of analytical method in quantification of active constituent. Ebeshi *et. al.,* in 2009 reported that a single method is not adequate to authenticate the quality of particular drug sample in post market surveillance, therefore, manufacturers or regulatory authorities should use more than one analytical method to evaluate the quality of pharmaceutical products.

The percentage content of ASA must fall within 95-105% as per the official compendium specification for tablets with average weight above 250 mg (British Pharmacopoeia, 2009). Mean average content of analyzed ASA tablets by colorimetric method was found to be 92.2% for brand A and 100% for brand B. The amount of active ingredient in brand A is less than 95% of the labeled amount as required by BP, so it failed the content uniformity test by this method. Brand A also failed to meet the official compendium requirement for content uniformity by volumetric method of analysis. Mean average content of ASA in brand A tablets by visual acid base titration method was found to be 93.57%. On the other hand, brand B passed the content uniformity test by both methods as it conformed to the official limit of 95-105%. The p -value obtained by student's *t*-test was found to be non significant as it was less than 0.05. The results obtained by two different methods of chemical analysis were almost similar, hence it could be concluded that any of these two methods could be employed to determine the content of ASA in ASA tablets.

CONCLUSION

Quality control is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the customer. Two different brands of ASA tablets were evaluated using quality control tests of (Hardness, Friability, Diameter ,Weight variation, Disintegration time, and content uniformity) with aim to assess whether these two brands are pharmaceutically equivalent or not. The results obtained were compared with British Pharmacopoieal standard specifications.

The results indicated that brand B met all requirements of the quality control tests (official and unofficial), although brand A passed all the official and unofficial tests but failed the content uniformity test as its mean drug content was found to be outside the compendial tolerance limit i.e. (95-105%) by both the methods of analysis.

There is not much difference in the pricing of both brands and thus these are equally prescribed by the prescribers in Oman. However, results of this pilot study suggest that the two brands of ASA differ in the content of API, so are not pharmaceutically or chemically equivalent which warrants manufacturer and drug regulatory authorities to step up the quality control and cGMP procedures.

Further detailed study on large batches of tablets should be carried out to confirm the finding of this pilot study to ensure safety, quality and efficacy of this commonly used house hold drug.

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