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QUALITY ANALYSIS STUDY ON MARKET PREPARATION OF METFORMIN TABLET AVAILABLE IN BANGLADESH

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ABSTRACT

Tablet is a pharmaceutical unit dosage form. Various brands of same dosage forms are available in the market with the common claim that they are all complies the standard pharmacopoeia. Total five different brands of Metformin tablets from different manufacturers were selected in the study. Dissolution testing was conducted according to USP from each brand for 25 minutes by using dissolution testing apparatus USP type-I (Basket). The tablets were subjected to various post-production tests such as hardness, physical parameters like weight variation, chemical parameters like assay, disintegration also considered for this study. Assay and Dissolution was checked by using a UV Spectrophotometer where Phosphate Buffer was used as dissolution medium. From the analysis of the results, it was observed that there was a considerable variation in the dissolution rates and also in the pattern of hardness, assay, friability, disintegration and weight of tablets. The disintegration, hardness and weight variation test of Tablets were performed as mentioned in BP or USP in world class equipment. All the results of these tests were matched USP standards. If the disintegration time, hardness, weight variation of Tablets varies a lot from the standard time, the tablets will not be able to show the desired therapeutic effect on time in the patients, which in result will increase the risk of patients. From the analysis of the results, this was observed that there was a considerable variation in the dissolution rates and also in the pattern of hardness, assay, friability, disintegration and weight of tablets.

KEYWORDS: Metformin tablets, disintegration & dissolution, analysis, USP, comply.

INTRODUCTION

Over 90% of the tablets manufactured today are ingested orally. The administration of drugs through oral route is the most common and the easiest way of administering a drug. The objective of this work is to evaluate the comparative efficiency of some market preparations of metformin ER by using in vitro methods. Metformin ER (a long-acting, extended-release version of metformin) is used to treat type 2 diabetes. The drug works by decreasing the amount of sugar that the liver makes and by decreasing the amount of sugar absorbed into the body. The medication comes in the form of a tablet that should be taken once a day with evening meal (Princeton NJ, 2006; FDA, 2007).Metformin HCl is an orally administered anti-diabetic drug from the Biguanide class. It is recommended as the first-line drug of choice for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus.

Official Tests: Weight Variation, Disintegration, Dissolution & Drug content.

Non-Official Tests: Hardness &Friability.

MATERIALS AND METHOD

Chemicals

Metformin tablets, Distilled water, Concentrated Hydrochloric Acid, Sodium Hydroxide & Potassium di-hydrogen phosphate.

Name of the Instruments

Electronic Balance (Shimadzu), Tablet Hardness Tester (Monosanto Type), Digital Friability Test Apparatus (INTECH), Digital Tablet Disintegration Test Apparatus (INTECH), Tablet Dissolution Test Apparatus (VEEGO), UV- Visible Spectrophotometer (UVmini-1240, Shimadzu), pH Tester (MW101 pH Meter), Ultrasonic Cleaner (Takashi, Eumax).

Glass and Plastic Wares

Pipette (1mL, 10 mL), Volumetric Flask (500 mL, 250 mL), Funnel (Pyrex Glass, England), UV-Pyrex Cell(1 cm)(England), Beaker (1000 mL, 900 mL, 500 mL, 250 mL),Dropper (5mL), Stirrer, Measuring Cylinder (1000 mL, 250 mL, 10 mL).

DETERMINATION OF WEIGHT VARIATION

Principle

The following formula is used,

Weight Variation = (IW – AW)/AW x100%

Where, IW = Individual weight of tablet & AW= Average weight of tablet.

$$\% \text{ of Deviation } (+) = \frac{\text{Maximum Weight of a tablet} - \text{Average Weight of tablet}}{\text{Average Weight of tablets}} \times 100\%$$

$$\% \text{ of Deviation } (-) = \frac{\text{Average Weight of tablet} - \text{Minimum Weight of a tablet}}{\text{Average Weight of tablets}} \times 100\%$$

Procedure

Randomly each of the 20 tablets of five brands is selected. Each of the 20 tablets is weighed separately by using an electronic balance. All of the 20 tablets are weighed together and average weight is calculated individually by dividing it with 20. Weight variation of each tablet is calculated individually by using the formula mentioned in principle.

HARDNESS MEASUREMENT

Principle

The hardness of a tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of recipients used during formulation. If the tablet is too hard, the disintegration time is long and can't meet up the dissolution specification, if it's too soft, it can't withstand handling when dealing with processes such as coating or packaging and a hardness of 4Kg is usually well thought-out to be the minimum for satisfactory tablets. Oral tablets have a hardness of 4 to 10 kg; but, hypodermic and chewable tablets have a hardness of 3 kg and sustained release tablets have about 10-20 kg.

Procedure

The lower plunger is placed in contact with the tablet and zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded.

FRIABILITY TEST

Principle

The percent of friability of tablet can be determined by this following formula.

Friability = (IW – FW)/IW x 100%

Where, IW = Initial weight of all tablets & FW = Final weight of all tablets.

Acceptable Range According To USP

Conventional compressed tablets that loss less than 0.5% to 1% (after 100 revolutions) of their weight are generally considered acceptable.

Procedure

Each of the 10 tablets is weighed separately by using an electronic balance. The friability tester is then set for 4 min of 100revolutions and all the tablets are placed in the apparatus and it is turned on. During this period the tablets are exposed to rolling and repeated shocks resulting from free fall within the apparatus. When the device stops automatically the tablets are collected and weighed again.

DETERMINATION OF DISINTEGRATION TIME

Principle

Disintegration is a physical phenomenon of breaking of dosage form into small particle. For a drug, to be absorbed from a dosage form after oral administration it must undergo dissolution & the first important step toward this condition is usually the breakup of the tablet & this process is known as disintegration. The time that it takes a tablet to disintegrate is measured in a device described in the USP/NF. Disintegration is a measure of the time required under a given set of condition for a group of tablet to disintegrate into particles which will pass through 10 mesh screen. Generally, the test is useful for coating assurance of conventional dosage form.

Procedure

To test for disintegration time one metformin-500mg tablet is placed in each tube, and the basket rack is positioned in a 1-L beaker of water at 37℃, such that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descent not closer than 2.5 cm below the surface of the liquid on their upward movement and descent not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device is used to move the basket assembly coating the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test. These are placed on the top of tablets and impart an abrasive action to the tablets. The discs may not be meaningful or impart more sensitivity to the test, but they are useful for tablets that float. Here to create an acidic or basic media we are used 0.1N HCI or Buffer solution also used distilled water as the media.

DISSOLUTION STUDY OF METFORMIN TABLETS

Principle

Dissolution is the process by which a drug becomes dissolved in a solvent. In biological systems, drug dissolution is an important parameter prior to systemic absorption. Dissolution test is used to determine the dissolution rate of the active ingredients of solid dosage

forms (for example, tablets, capsules and suppositories). After oral administration, a tablet undergoes disintegration on and then the drug goes into the solution. The rate of absorption and bioavailability of the drug are directly related to the dissolution rate of the drug. Dissolution of a tablet is influenced largely by the pH of the absorption site as well as PKa of the drug.

DISSOLUTION METHOD

Dissolution Medium: Phosphate Buffer pH 6.8, Volume: 900 ml, Apparatus: USP type-I (Basket Method), Stirring Speed: 100RPM, Time: 25 min, Temperature: 37℃.

Spectro-photometric Condition

Blank: Phosphate Buffer (pH 6.8), Cell: 1 cm. Quartz, OD: 233 nm.

Preparation of Standard Solution

Firstly Weight and transferred accurately about 56 mg working standard of Metformin in to a clean & dry 200 ml standard volumetric flask. Then added about 100 ml phosphate buffer solution and mixed well. Added 5ml methanol and shaken well. Then transferred 2 ml of this solution into a 200ml volumetric flask and diluted it with 200 ml of distilled water.

Sample Preparation

900 ml of phosphate buffer was taken in the beaker and then the beaker was placed in the dissolution medium though each vessel. Allowed the medium to equilibrate to a temperature 37±0.5℃. Placed 1 tablet in to each vessel at the beginning of the test and then the pebble was immersed into the fluid before rotation. The motor was started and as a result the paddle was rotated at fixed rpm (100 rpm). After 25 minutes, the medium (sample) was filtered and then 2 ml of filtrate was taken and diluted to 200 ml with distilled water. The absorbance of the diluted solution was determined at the wavelength of 233nm. From the absorbance value the concentration of the drug in the medium after specific time was determined. The complete operation was repeated five times.

CONTENT/ ASSAY METHOD

Principle

To determine the content of metformin in each tablet UV spectrophotometric method was used. UV spectroscopic method is one of the instrumental analytical methods. It is widely used in industry, research purpose & in the clinical evaluation of many pharmaceutical dosage forms. It is relatively quick method. The principle of UV spectroscopic method is based on the Beer- Lambert low. This law stated that, absorbance or optical density is directly proportional to the amount of concentration in the sample. This law is valid only for the dilute solution. By UV spectroscopic method, we can either find out the amount of drug or chemical present in the sample by taking absorbance of standard substances of sample.

Reagent

Standard Metformin powder, Marketed Metformin Tablet, Distilled Water.

Name of the Instrument

UV spectrophotometer (UV mini – 1240, Shimadzu), Electronic Balance (Shimadzu).

Name of Apparatus

Beaker (1000 mL, 500mL), Pipette (10mL), Volumetric Flask (250mL, 500mL, 100mL).

Procedure

Preparation of Standard solution: Weighed and transferred accurately about 100mg working standard of metformin powder in a clean & dried 250 ml standard volumetric flask. Added about 100 ml of distilled water and diluted properly. Then transferred 1 ml of dilute solution into a 100 ml volumetric flask and added up to the mark with 100ml of distilled water.

Preparation of Sample solution: Each of 5 tablets in five brands of Metformin was diluted with 250 ml of dist. Water into a 250 mL volumetric flask. Then transferred 1 ml of this dilute solution into a 1000 mL volumetric flask and added distilled water up to 1000 ml. Then the solution was filtered through WHATMAN filter paper. During filtration, 20ml of the filtered solution was withdrawn. When the filtration was completed, solution was taken to determine the absorbance at 233 nm with a suitable spectrophotometer.

DISCUSSION AND RESULTS

Table1: Selected Tablet for Test.

SL. No.	Company Name	Brand Name
1	Square Pharmaceuticals Ltd.	Comet 500mg
2	Incepta Pharmaceuticals Ltd.	Nobesit 500mg
3	Beximco Pharmaceuticals Ltd.	Informet 500mg
4	Eskayef Bangladesh Ltd. Mirpur.	Glunor 500mg
5	Novartis (Bangladesh) Ltd.	Etform 500mg

BRAND NAME: Comet (500mg)
Weight Variation Test
Total weight of 20 tablets = 10919 mg, Average Wt (Aw) =545.95 mg, Maximum Wt (mg) =552 mg, Minimum Wt. (mg) = 535 mg
% of Weight Variation:

$$\text{Maximum (+)} = \frac{552 - 545.95}{545.95} \times 100\% = 1.10\%$$

$$\text{Minimum (-)} = \frac{545.95 - 535}{545.95} \times 100\% = 2.00\%$$

Hardness Test: Average Value of Hardness = 39.616N-cm or 4.040 kg-cm.

Friability Test: The value of Friability test = 0.811%.

Disintegration Time Test: Disintegration Time = 2 min to 10 min (0.1 N HCI), 1 min to 9 min (Phosphate Buffer) & 3 min to 12 min (Distilled Water).

Dissolution Test
Calculation of Standard Solution for Dissolution: Response Factor = 99.8 %.
% of Dissolution of 6 Comet 500 mg Tablets: Average of Dissolution =100.1%.

Content/Assay Test
Calculation of Standard Solution for Assay Method: Response Factor = 99.4%.
% of Content of Comet 500 mg Tablets: Average of Assay = 103.94%.

Table2: Final Result of Comet 500 mg Tablet Study (Square Pharmaceutical Limited Bangladesh)

Study Type	Study Result	USP Specification	Status
Weight Variation	Maximum = 1.108% Minimum = 2.006%	±5%	Complies
Hardness	Average = 39.616N-cm or 4.040 kg-cm	Within 4 to 10 kg-cm	Complies
Friability	0.811%	Not more than 1%	Complies
Disintegration	a. 2 min to 10 min (0.1 N HCI) b. 1 min to 9 min (Phosphate Buffer) c. 3 min to 12 min (Dist. Water)	Within 15 minutes	Complies
Dissolution	Average of Dissolution = 100.1%	Within 98 % to 102 %	Complies
Assay	Average of Assay = 103.94%	Within 95% to 105%	Complies

BRAND NAME: Nobesit (500 mg)
Weight Variation Test
Total weight of 20 tablets = 11253 mg, Average Wt., Aw (mg)= 562.65 mg, Maximum Wt. (mg) = 588 mg, Minimum Wt. (mg) = 535 mg.
% of Weight Variation

$$\text{Maximum (+)} = \frac{588 - 562.65}{562.65} \times 100\% = 4.50\%$$

$$\text{Minimum (-)} = \frac{562.65 - 535}{562.65} \times 100\% = 4.91\%$$

Hardness Test: Average Value of Hardness = 42.463N-cm or 4.330 kg-cm.

Friability Test: The value of Friability test = 0.569%.

Disintegration Time Test: Disintegration Time = 3 min to 5 min (0.1 N HCI), 1 min to 3 min (Phosphate Buffer) & 2 min to 6 min (Distilled Water).

Dissolution Test
Calculation of Standard Solution for Dissolution: Response Factor = 100 %.
% of Dissolution of 6 Nobesit 500 mg Tablets: Average of Dissolution = 100.5%.

Content/Assay Test
Calculation of Standard Solution for Assay Method: Response Factor = 99.4%.
% of Content of Nobesit 500 mg Tablets: Average of Assay = 101.29%.

Table3: Final Result for Nobesit 500 mg Tablet Study (Incepta Pharmaceutical Limited Bangladesh).

Study Type	Study Result	USP Specification	Status
Weight Variation	Maximum = 4.50% Minimum = 4.91%	±5%	Complies
Hardness	Average = 42.463 N-cm4.330 kg- cm	Within 4 to 10 kg-cm	Complies
Friability	0.569%	Not more than 1%	Complies
Disintegration	a. 3 min to 5 min (0.1 N HCI) b. 1 min to 3 min (Phosphate Buffer) c. 2 min to 6 min (Dist. Water)	Within 15 minutes	Complies
Dissolution	Average of Dissolution = 100.5%	Within 98 % to 102 %	Complies
Assay	Average of Assay = 101.29 %	Within 95% to 105%	Complies

BRAND NAME: Informet (500 mg)

Weight Variation Test

Total weight of 20 tablets = 13982 mg, Average Wt (Aw) = 699.1 mg, Maximum Wt (mg) =708 mg, Minimum Wt. (mg)= 691 mg.

% of Weight Variation

Maximum (+) = $\frac{708 - 699.1}{562.65} \times 100\% = 1.27\%$

Minimum (-) = $\frac{699.1 - 691}{699.1} \times 100\% = 1.16\%$

Hardness Test: Average Value of Hardness =41.777N-cm or 4.260 kg-cm.

Friability Test: The value of Friability test = 0.167%.

Disintegration Time Test: Disintegration Time = 1 min to 4 min (0.1 N HCI), 0 min to 1 min (Phosphate Buffer) & 2 min to 6 min (Distilled Water).

Dissolution Test

Calculation of Standard Solution for Dissolution: Response Factor = 99.5%.

% of Dissolution of 6 Informet 500 mg Tablets: Average of Dissolution = 100.5%.

Content/ Assay Method

Calculation of Standard Solution for Assay Method: Response Factor= 99.4%.

% of Content of Informet500mg Tablets: Average of Assay = 105.68%.

Table 4: Final Result For Informet 500 mg Tablet Study (Beximco Pharmaceutical Limited Bangladesh).

Study Type	Study Result	USP Specification	Status
Weight Variation	Maximum = 1.273% Minimum = 1.159%	±5%	Complies
Hardness	Average = 41.777N-cm or 4.260 kg-cm	Within 4 to 10 kg-cm	Complies
Friability	0.167%	Not more than 1%	Complies
Disintegration	a. 1 min to 4 min (0.1 N HCI) b. 0 min to 1 min (Phosphate Buffer) c. 2 min to 6 min (Dist. Water)	Within 15 minutes	Complies
Dissolution	Average of Dissolution = 100.5%	Within 98 % to 102 %	Complies
Assay	Average of Assay = 105.68%	Within 95% to 105%	Complies

BRAND NAME: Glunor (500mg)

Weight Variation

Total weight of 20 tablets = 14561 mg, Average Wt (Aw) = 728.05 mg, Maximum Wt. (mg) = 738, Minimum Wt. (mg) = 716.

% of Weight Variation.

Maximum (+) = $\frac{738 - 728.05}{728.05} \times 100 = 1.37\ \%$

Minimum (-) = $\frac{728.05 - 716}{728.05} \times 100 = 1.66\%$

Hardness Test: Average Value of Hardness =41.286N-cm or 4.210 kg-cm.

Friability Test: The value of Friability test = 0.384 %.

Disintegration Time Test: Disintegration Time = 1 min to 6 min (0.1 N HCI), 0 min to 8 min (Phosphate Buffer) & 1 min to 9 min (Distilled Water).

Dissolution Test

Calculation of Standard Solution for Dissolution: Response Factor = 100.1%.

% of Dissolution of 6Glunor 500mg Tablets: Average of Dissolution = 100.3%.

Content/ Assay Test

Calculation of Standard Solution for Assay Method: Response Factor = 99.4%.

% of Content of Glunor 500 mg Tablets: Average of Assay = 103.16%.

Table5: Final Result for Glunor 500 mg Tablet Study (Eskayef Bangladesh Ltd. Mirpur.)

Study Type	Study Result	USP Specification	Status
Weight Variation	Maximum = 1.367% Minimum = 1.655%	±5%	Complies
Hardness	Average = 41.286N-cmor 4.210 kg-cm	Within 4 to 10 kg-cm	Complies
Friability	0.384%	Not more than 1%	Complies
Disintegration	a. 1 min to 6 min (0.1 N HCI) b. 0 min to 8 min (Phosphate Buffer) c. 1 min to 9 min (Dist. Water)	Within 15 minutes	Complies
Dissolution	Average of Dissolution = 100.3%	Within 98 % to 102 %	Complies
Assay	Average of Assay = 103.16%	Within 5% to 105%	Complies

BRAND NAME: Etform (500mg)

Weight Variation

Total weight of 20 tablets = 10904 mg, Average Wt (Aw) = 545.2 mg, Maximum Wt. (mg) = 564 mg, Minimum Wt. (mg) = 533 mg.

% of Weight Variation.

$$\text{Maximum (+)} = \frac{564 - 545.2}{545.2} \times 100 = 3.45\ \%$$

$$\text{Minimum (-)} = \frac{545.2 - 533}{545.2} \times 100 = 2.24\%$$

Hardness Test: Average Value of Hardness = 40.011N-cm or 4.08 kg-cm.

Friability Test: The value of Friability test = 0.56%.

Disintegration Time Test: Disintegration Time = 2 min to 5 min (0.1 N HCI), 1 min to 5 min (Phosphate Buffer) &2 min to 5 min (Distilled Water).

Dissolution Test

Calculation of Standard Solution for Dissolution: Response Factor = 99.9%.

% of Dissolution of 6Etform 500mg Tablets: Average of Dissolution =100.1%.

Content/ Assay Test

Calculation of Standard Solution for Assay Method: Response Factor = 99.4%.

% of Content of Etform 500mg Tablets: Average of Assay = 102.9%.

Table 6: Final Result For Etform 500 mg Tablet Study (Novartis Bangladesh Ltd.)

Study Type	Study Result	USP Specification	Status
Weight Variation	Maximum = 3.448% Minimum = 2.238%	±5%	Complies
Hardness	Average = 40.011 N-cm or 4.08 kg-cm	Within 4 to 10 kg-cm	Complies
Friability	0.56%	Not more than 1%	Complies
Disintegration	a. 2 min to 5 min (0.1 N HCI) b. 1 min to 5 min (Phosphate Buffer) c. 2 min to 5 min (Dist. Water	Within 15 minutes	Complies
Dissolution	Average of Dissolution = 100.1%	Within 98 % to 102 %	Complies
Assay	Average of Assay = 102.9%	Within 95% to 105%	Complies

CONCLUSION

Our experiment shows that, the five brands of Metformin tablets comply in all of the tests. According to USP. Experiment shows that, Weight Variation is within ±5%, Hardness Limit 4 to 10 kg/cm2, Friability is not more than 1%, dissolution range is within 98 % to 102 % within 25 minutes and these five brands comply in dissolution test and Assay. Within these tests, we are ensure that the five market products will benefit the patient's required therapeutic effect and recuperate the patient's disease condition.

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