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COMPARATIVE EVALUATION OF PREDNISOLONE 5MG TABLETS MARKETED IN BANGLADESH

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ABSTRACT

The aim of the present study is to determine the quality and to correlate with other different brands of pharmaceutical products marketed in Bangladesh for the healthcare of patients suffering from different respiratory inflammation like asthma, and auto-immune disorders. The experiment is done to evaluate and compare the physicochemical equivalence of different brands of Prednisolone 5mg tablet. These tablets were tested through statistical methods in accordance with the BP and USP like weight variation, thickness, hardness, friability, disintegration, in-vitro dissolution and HPLC assay. The in vitro dissolution studies of Prednisolone 5 mg tablets were carried out in pH 7 distilled water for 30 minutes using USP-II method whose absorbance were taken at 246 nm using UV spectrophotometry. Six samples showed poor in-vitro dissolution which were non-equivalent to the USP monograph specification giving Prednisolone content less than 75%. The percentage content of active ingredient of different brands were tested using HPLC assay. Samples showed values within the specifications (90-110%) except some of the companies. Two samples did not undergo disintegration at all when given in the disintegration tester. However, no major problem was found in others physical parameters like tablet weight variation, thickness, hardness and friability. Finally from the experiment we can conclude that 50% of the companies in the urban area are substandard, whereas 50% companies provide standard drugs.

KEYWORDS: Dissolution test, Prednisolone, Quality control of tablets.

1. INTRODUCTION

1.1 Structural Formula

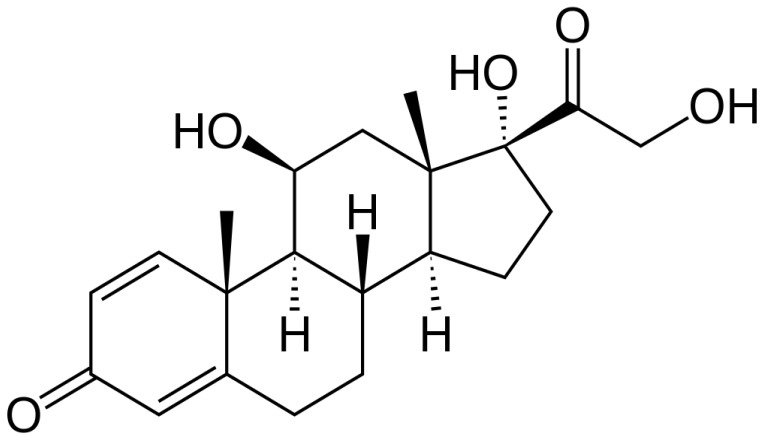

Figure 1: ***Structure of prednisolone***[14]

Prednisolone is a synthetic glucocorticoid, a derivative of cortisol which is used to treat a variety of inflammatory and auto-immune conditions. It is the active metabolite of drug prednisone and it is used in patients with hepatic failure as they are unable to metabolize prednisone to prednisolone.[1] Prednisolone is generally safe for human use at recommended doses. But, overdoses of prednisolone can cause sodium and water retention and adverse cardiovascular risk.[2]

The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable.[3] The efficacy of pharmaceutical dosage forms generally depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary.[4-5] Dissolution test is one of the in vitro tests usually employed to assess the quality of oral pharmaceutical solid dosage forms such as tablets and capsules. In vitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor formulation quality from batch to batch, predict the in vivo performances and also serve as a surrogate for bioavailability and bioequivalence.[6-7] Therefore, it was decided to carry out the comparative evaluation of in vitro dissolution qualities of various commercially available Prednisolone tablet samples. Prednisolone tablets of 5mg were chosen for the study. Statistical assessment of various in vitro dissolution parameters was conducted to establish if there were any significant differences among them.

The WHO has been tracking and documenting the incidences of substandard drugs. The records show that problems of substandard and counterfeit drugs are on increase as 50% of all reported cases occurred in the period 1993 to 1997. Most of these incidences (70%) were reported in developing countries. The report identifies the causes of the poor quality of drugs: in about 50% of all the cases the formulations did not contain any drug, 20% contained the wrong active ingredient and 10% the wrong amount of the active ingredient. Only in 5% of the reported incidences did the drugs contain the right active ingredient in the correct amounts, but were judged substandard by failing other quality tests.[8]

Drug products that are biopharmaceutically and chemically equivalent must be identical in their quality, strength, purity and active ingredient release profile. They must to be in the same dosage form and intended for the same route of administration.[9] Dissolution testing of drug product is an important criterion in assessing the quality control to monitor batch to batch consistency of drug release.[10] The variations in the drug release among some generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution rate determination used also for prediction of in-vivo bioavailability in most oral preparations.[11, 12]

Prednisolone was obtained from Prescription Aid, Banani Dhaka. The prednisolone tablets (5 mg) were purchased from local market and coded as Sample 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12. All commercial tablets were of same manufacturing year, and were recently manufactured.

2. MATERIALS AND METHODS

Prednisolone 5mg tablets of twelve different brands were purchased. All the products were manufactured within six months from the date of study. The products were coded as sample number 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12. The labeled shelf-life of all products were 36 months. The product was evaluated for weight variation, thickness variation, hardness test, friability test, disintegration test and dissolution test. Different samples were collected from local pharmacy of Dhaka city. The list of samples are given below.

Table-1: Batch number and expiry date of various prednisolone tablets used in the study

Sample Number	Batch No.	Expiry date
Sample 1	602-28-50	APR 16
Sample 2	602-28-50	MAY 16
Sample 3	13059 E0816	AUG
Sample 4	13059 E0816	AUG 16
Sample 5	B166	AUG 16
Sample 6	B167	AUG 16
Sample 7	336E0916	SEP 16
Sample 8	346E0916	SEP 16
Sample 9	408002	JULY 16
Sample 10	408004	SEP 16
Sample 11	B06E02 2017	FEB 17
Sample 12	B10E02 2017	FEB 17

2.1 Weight Variation

The significance of this test is to ensure that the tablets in each batch are within appropriate range, size and contents are calculated on average tablet weight basis. It was found that all the tablets passed the USP specifications for weight variation as none of the brands deviated by upto ±5% from the mean value. Weight variation gives a rough idea of content uniformity, but not a confirmatory test.

2.2 Friability

Friability is another important parameter that is related to hardness, disintegration and dissolution. According to the USP, the allowed limit of friability is not more than 1.0 % of weight Loss. The friability was carried out for all the samples. It was not less than 1% for any of the samples.

2.3 Hardness

In the pharmaceutical industry, hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. However, if the hardness exceeds a certain limit, it increases the disintegration time, which ultimately affects the bioavailability.[13] Hardness is not an official test so there is no such a compendial limit for hardness but a crushing strength of between 4 kg/cm2 to 10 kg/cm2 is considered minimum requirement for a satisfactory tablets. The average hardness of the local and multinational brands was within the limits.

2.4 Disintegration

Disintegration could be related to dissolution and similarly availability of drug to body (absorption) and finally the therapeutic efficacy of product. The result showed that disintegration time of all the selected tablets was found to be within specified limits of USP and BP. According to USP, uncoated tablets have disintegration time standards as low as 5 minutes. For sample 3 and 4 it is seen no disintegration takes place. Which shows the drug does not undergo dissolution and is substandard.

2.5 Dissolution test

Release rate of Prednisolone tablet is carried on according to the general procedure of United States Pharmacopoeia (USP).[14] Samples of dissolution fluid are withdrawn and analyzed by UV Spectrophotometer. The measurement is done at the wavelength at 246nm. By comparing with absorbance of standard solution, the amount of active Prednisolone in tablets released is calculated.

In-vitro dissolution studies were carried out using a dissolution apparatus USP (Paddle type) at a paddle speed of 50 rpm. The dissolution medium was distilled water which was maintained at 37 ± 0.5 °C. In all dissolution experiments, 10 ml of dissolution samples were withdrawn and replaced with equal volume of distilled water, at regular intervals. Collected dissolution samples were used for determination of released prednisolone concentrations by using a UV-VIS spectrophotometer (U.V. 2440 Double beam spectrophotometer, SHIMADZU Corporation, JAPAN) at 246 nm wavelength against a blank.

$$\% \text{ Prednisolone content} = \text{Absorbance of sample} \times \frac{\text{Wt. of Std.} \times \text{Av. Wt. of tablets} \times 100}{\text{Abs. of Std.} \times \text{Wt. of sample}}$$

Preparation of Standard Solution

50mg of working standard of Prednisolone was weighed and transferred into a clean and dry 100ml volumetric flask. Then 90ml of distilled water was added to the volumetric flask and shaken. The volumetric flask is put in the sonicator for 5 minutes and made up to the mark. From the above solution 10ml is taken in another clean and dry 100ml volumetric flask and 50ml distilled water is added to make the solution. The solution is put in sonicator for 5minutes and the volume is adjusted to make up the mark. Concentrations of 1mg.ml, 2mg/ml, 3mg/ml, 4mg/ml and 5mg/ml.

Preparation of sample solution

900ml of distilled water was placed into each of six dissolution vessels and the temperature was set to 37°C(±0.5). Weighed tablets of Prednisolone were transferred to each six baskets. The baskets were immersed into the medium to a distance 25±2 mm between the basket and bottom of the vessel. The apparatus was started to operate at the specified rpm. At the end of 1st hour, 10ml samples were withdrawn from each vessel and filtered through Whatman filter paper discarding first few ml of filtrate. The withdrawn quantity of samples was replaced by fresh dissolution medium to maintain constant volume of dissolution medium. 4ml of the filtrate were diluted with distilled water into 10ml volumetric flask and mixed well.

Then the absorbance of the above solution in a 1cm silica cell were measured at the wavelength of maximum absorbance at 246nm by UV-visible spectrophotometer using distilled water as blank.

2.6 HPLC Assay

Principle

Assay test for prednisolone was done as per USP monograph. A prepared standard and sample solution are injected consequently into suitable column of High Performance Liquid Chromatography (HPLC). The content of Prednisolone present in each sample is calculated by comparing both the peak areas of active Prednisolone present in the standard preparation and prepared sample.

Standard preparation

About 5 mg of USP Prednisolone RS, accurately weighed and then transferred, to a 100-ml volumetric flask and dissolved in 5.0 ml methanol. Then 20.0 ml of internal standard solution was added and mix. Finally diluted with water-saturated chloroform to 100.0 ml and mixed properly.

Sample preparation

Approximately 5mg Prednisolone tablets were weighed and made fine powder by crushing with mortar and pestle. Then the fine powdered sample was transferred into a clean and dry 100ml volumetric flask. And dissolved in 5.0 ml methanol. Then 20.0 ml of internal standard solution was added and mix. Finally diluted with water-saturated chloroform to 100.0 ml and mixed properly.

20µg/ml. the solution was mixed well and injected into four vials through 0.45µ disk filter. These were called as sample solution using the liquid chromatograph (SHIMADZU Corporation) equipped with a 254 nm detector and a 4-mmx30-cm column. The above procedure was followed for twelve different companies and their tablets

3. RESULTS AND DISCUSSIONS

In this study physicochemical properties of twelve brands of Prednisolone (5mg) tablets were evaluated in order to identify the relative difference in quality parameters and its effect on the release of drug dosage form.

Table 2: ***Average weight, thickness, hardness, friability and disintegration time of various prednisolone samples used during the study.***

Sample number	Avg. Weight (mg)	Thickness(mm)	Avg. Hardness (kg)	Friability (%)	Disintegration time(minutes)
1(local)	0.1351	0.3	2.861	0.007	8
2(local)	0.1353	0.3	2.838	0	7
3(local)	0.1779	0.35	9.736	0	Did not disintegrate
4(local)	0.1779	0.35	10.884	0	Did not disintegrate
5(multi-national)	0.099	0.2	5.313	0	2
6(multi-national)	0.099	0.2	5.034	0	2
7(local)	0.0653	0.2	4.224	0.006	3
8(local)	0.0656	0.2	4.53	0	3
9(local)	0.1517	0.31	2.624	0	6
10(local)	0.1515	0.32	2.734	0	6
11(local)	0.1517	0.33	3.636	0	8
12(local)	0.1536	0.31	3.682	0	8

Table 3: ***Percentage of prednisolone content of tablets of different samples***

% Prednisolone content												
Tablet number	**Sample 1 (local)**	**Sample 2 (local)**	**Sample 3 (local)**	**Sample 4 (local)**	**Sample 5 (multi-national)**	**Sample 6 (Multi-national)**	**Sample 7 (local)**	**Sample 8 (local)**	**Sample 9 (local)**	**Sample 10 (local)**	**Sample 11 (local)**	**Sample 12 (local)**
1	99.66	79.98	82.83	83.28	96.03	97.81	95.65	93.36	91.85	82.37	76.89	76.22
2	97.62	77.93	81.52	80.52	97.78	97.43	97.38	99.92	91.75	82.32	76.87	75.76
3	97.98	78.3	86.52	84.02	93.75	96.34	93.38	95.73	91.8	82.23	74.64	75.96
4	96.74	77.05	80.64	83.34	93.57	95.72	93.2	95.37	91.75	82.16	73.88	75.72
5	95.9	76.21	82.49	83.71	92.43	94.98	92.06	96.55	91.72	82.09	72.75	75.59
6	95.06	75.37	84.33	84.08	91.29	94.25	90.93	97.74	91.7	82.02	71.63	75.46
Average	96.86	77.17	82.71	82.78	93.73	95.83	93.36	96.00	91.75	82.17	74.04	75.74
standard deviation	1.63	1.64	2.11	1.33	2.38	1.38	2.37	2.23	0.05	0.13	2.15	0.27
relative standard deviation	0.02	0.021	0.025	0.016	0.025	0.014	0.025	0.023	0.001	0.002	0.029	0.004

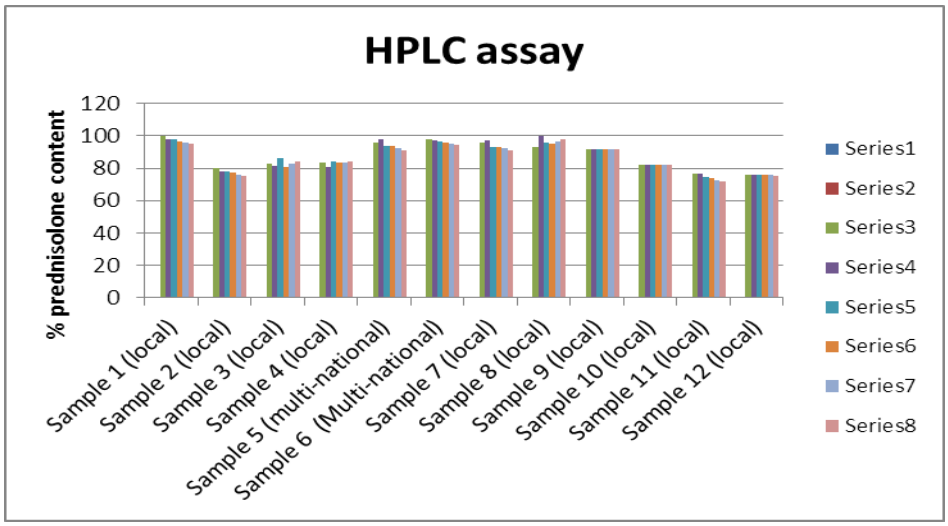

Figure 1: ***Bar chart showing the prednisolone content of different samples.***

Test for percentage of content is based on the assay of the individual content of active ingredient of a number of single dose units. Six samples of Prednisolne tablets multinational and local brands, contained the Prednisolone within 100 ±10 % of the labeled claim. The USP specifications for assay are that the Prednisolone contents should not be less than 90 %[14] and not more than 110%. Therefore, the assay results establish the presence and compendial quality of the drug in all products. The results of HPLC analysis are presented in the bar chart above, from the above bar chart we can see that the percentage of Prednisolone content varies from one sample to another. The lowest percentage content of Prednisolone was found of sample 12 was 75.21%. The highest percentage content of Prednisolone was found for sample 8 and that was 99.92%.

Table 4: ***Table for in-vitro dissolution shows the percentage of drug released of different samples***

% Drug Released												
Sample Number	**Sample 1 (local)**	**Sample 2 (local)**	**Sample 3 (local)**	**Sample 4 (local)**	**Sample 5 (Multi-national)**	**Sample 6 (Multi-national)**	**Sample 7 (local)**	**Sample 8 (local)**	**Sample 9 (local)**	**Sample 10(local)**	**Sample 11 (local)**	**Sample 12 (local)**
1	79.4	61.78	12.2	11.45	70.74	78.56	94.14	76.58	76.34	56.58	46.75	48.25
2	74.82	62.29	11.54	10.85	79.57	79.85	90.74	75.95	78.38	55.95	48.71	49.78
3	72.46	60.08	10.86	12.47	72.46	72.35	92.1	76.75	74.82	56.75	49.57	48.62
4	71.95	69.57	12.56	12.32	76.85	75.27	95.84	75.85	78.81	55.85	48.35	49.35
5	78.67	60.76	11.65	10.75	71.65	72.85	92.65	72.59	78.65	52.59	47.65	48.25
6	79.67	61.61	12.45	11.95	72.21	70.32	93.52	73.85	77.52	54.81	49.25	48.72
7	70.65	60.25	10.98	10.85	75.85	71.2	92.85	75.25	70.95	55.25	48.45	49.65
8	72.45	60.59	11.54	11.35	78.65	79.85	91.65	79.57	72.56	59.57	49.51	50.25
Average	74.52	61.89	11.63	11.42	74.30	74.51	92.69	75.44	75.44	55.55	48.33	49.01
Standard Deviation	3.70	3.11	0.64	0.68	3.41	3.92	1.58	2.08	2.97	1.97	0.97	0.75
Relative Starndard Deviation	4.93	5.00	5.42	5.92	4.56	5.23	1.70	2.74	3.90	3.52	1.99	1.53

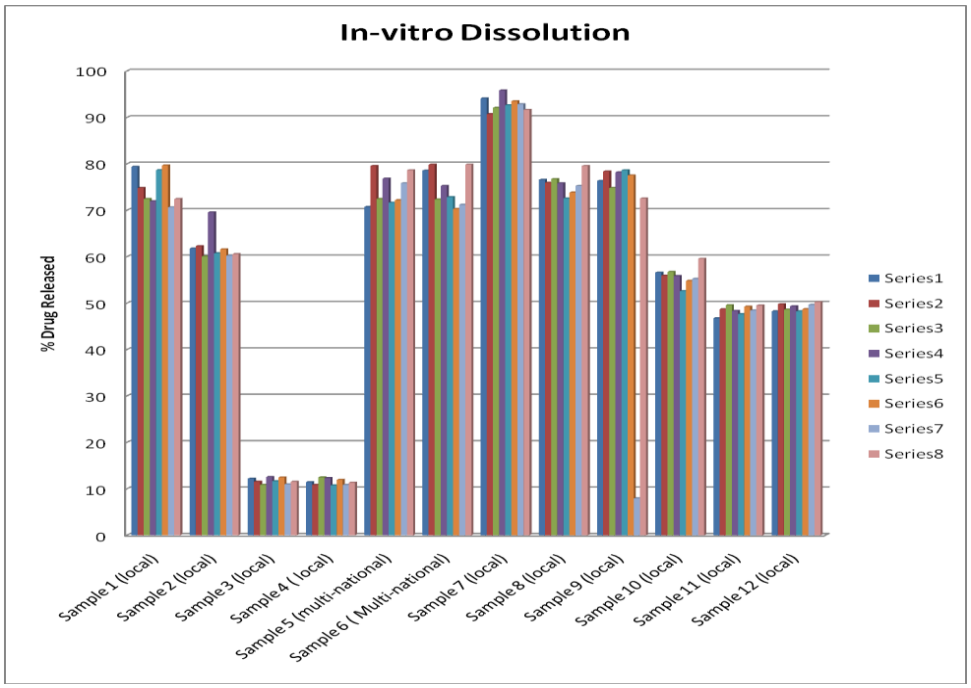

Figure 2: ***Barchart of in-vitro dissolution of Prednisolone tablets of different samples.***

Twelve brands of Prednisolone tablets which are commercially available in Bangladesh were subjected to a number of quality control tests in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of weight, friability, hardness, disintegration and dissolution tests as well as chemical content determination. All the brands used were within their shelf-life at the time of study.

The weight variation for twelve brands of Prednisolone tablets gave values that comply with the USP specification. Using the hardness tester, the strength of the tablets was tested. The maximum hardness was given by sample 4 which was 10.88 kg. The lowest hardness was given by sample 9 which was 2.6 kg as can be seen in Table 2.

The friability test is most important criteria for uncoated tablets (during and after manufacture) to examine that the tablets have a good withstand strength for transportation, packaging, shipping and coating. All the tested samples in this study are uncoated tablets. The friability was less than 0.006%, which is highly satisfactory. Samples 2, 3, 4, 5, 6, 8, 9, 10, 11, and 12 did not have any loss after going through the friability test.

CONCLUSION

In conclusion it can be said that the different brands of well reputed local pharmaceutical companies can be compared with that of multi-national companies. Only six brands passed

the dissolution test, tablets of six brands where below 50% as well as in HPLC assay shows some of the companies are below 90%. Two samples did not undergo disintegration at all that shows that the tablets are substandard. However, no major problem was found in tablet variation, thickness, friability and hardness. From the experiment we can conclude that 50% of the companies in the urban area are substandard, whereas 50% companies provide standard drugs. As in Bangladesh not only in rural areas but also in urban areas more medicine is required of high standard as more patients require better healthcare. However, products of some less known local pharmaceutical industry needs improvements in quality and should be strictly monitored for manufacturing of substandard dosage forms.

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