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COMPARATIVE EVALUATION OF PREDNISOLONE 5MG IMMEDIATE RELEASE TABLETS MARKETED IN SUDAN

A thesis submitted in partial fulfillment for the degree of M.Sc

of pharmaceutical technology

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DEDICATION

I dedicate this thesis to my parents, wife, brothers, sisters, and friends.

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ABSTRACT

Prednisolone is a type of medicine known as corticosteroid or steroid. Prednisolone is used to treat a wide range of health problems including allergies, blood disorders, skin diseases, infections, certain cancers and to prevent organ rejection after a transplant.

The aim of the present study is to determine the quality of Prednisolone 5mg immediate release tablet marketed in Sudan to compare the different brands. It also aims to ensure that the patients take an appropriate healthcare according to quality.

The tests were done to three different brands according to general procedure of BP & USP. The tests are weight variation, friability, disintegration, and assay by HPLC. Assays were carried out according to USP, other tests which are weight variation, friability test and disintegration were carried out according to BP [2012].

The results of content uniformity of prednisolone 5mg for brand (A), (B) and (C) were found (85.38%), (85.15%), and (84.36%) respectively. The relative standard deviations were found (1.1%), (0.1%) and (0.1%) respectively. The % loss of friability were found (0.04%), (0.55) and (0.03%) respectively. The disintegration times were found (6:27min), (7sec), and (18sec) respectively.

The results of assay were found out of specification. The results of other tests (weight variation, friability test and disintegration) were within specifications.

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1. Introduction

1.1.1 What is Prednisolone?

Prednisolone is a type of medicine known as corticosteroid or steroid. Corticosteroids are not the same as anabolic steroids. [1]

Prednisolone is used to treat a wide range of health problems including allergies, blood disorders, skin diseases, infections, certain cancers and to prevent organ rejection after a transplant. It helps by reducing inflammation. [1]

Prednisolone is available only on prescription a tablets and as liquid to drink. It can also be given by injection but this is usually only done in hospital. [1]

1.1.2 Drug profile

Chemical structure

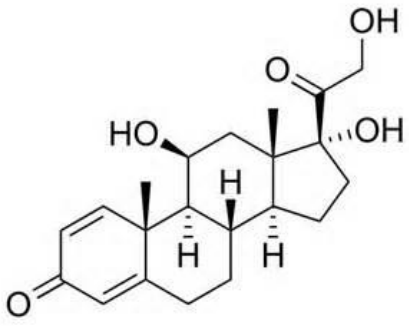

Figure1.1 Chemical structure of prednisolone [2].

The appearance of prednisolone white to white crystalline powder, molecular formula of $C_{21}H_{28}O_5$. Prednisolone has an aqueous solubility from 0.22 to 0.24 mg/ml. [3, 4], and it is class1 [highly soluble and highly permeable] according to BSC systems [5], melting point at 235°c, polymorphism of two forms have been characterized for prednisolone. Prednisolone, also forms solvates with water and chloroform (pseudo-polymorphism) [6]. Partition Coefficient: LogP values of 1.59 and 1.62 have been reported. [3].

1.1.3 Pharmacokinetics properties

1.1.3.1 Absorption and Bioavailability (BA)

Following oral intake prednisolone is rapidly absorbed from the GI tract. The systemic availability is almost complete and reported to range from 75% to 98%, Maximum serum concentrations occur within 1–2 h after administration of a single dose. [7]. Food intake prolongs the time to peak concentration, but does not affect the extent of absorption. [8].

1.1.3.2 Distribution

The volume of distribution of prednisolone was reported as 0.22–0.70 L/kg. With increasing dose, the volume of distribution prednisolone increases, due to a shift in a larger fraction of the body burden from the plasma compartment to other body tissues or to sites of greater metabolic activity [9].The concentration-dependent binding of prednisolone to the plasma proteins (i.e. Transcortin and Albumin) results in the dose-dependent nonlinear pharmacokinetics observed for prednisolone [7].

Distribution and elimination of prednisolone have been described in terms of a two-compartment open model, with rapid distribution within the first half-hour followed by a slower terminal elimination phase [7].

Prednisolone is able to penetrate the blood br ain barrier, reaching about 1/10 of the serum concentration in cerebrospinal fluid. Like all gluco-corticosteroids, prednisolone crosses the placenta [10].The use of prednisolone is usually compatible with breast feeding [11].

1.1.3.3 Elimination (Metabolism and Excretion)

Prednisolone is pharmacologically active and maybe metabolized in a variety of tissues, including liver, lung, kidney, and skin [10].The serum half-life of prednisolone is known to be 2–4 h [7]. Prednisolone is cleared from the body primarily by hepatic metabolism by hydroxylation and reduction forming metabolites which conjugate with glucuronic acid and sulfate [7].The clearance of prednisolone is dose-dependent [9].

Due to the concentration-dependent protein binding, that is, at high doses the increased free fraction of prednisolone is reflected in a greater plasma clearance and apparent volume of distribution. The total body clearance of prednisolone has been reported to be111 ml/min/1.73 m2 for a 5 mg dose of prednisolone.[9].Renal elimination comprises 40% of total elimination.[12].The mean elimination half-life increases with the dose and

ranges from 2.1 to 3.5h.The half-life in children is shorter than that recorded in most adult studies.[7].

1.2 Rationale of study

Many Sudanese pharmaceutical manufacturers produce a prednisolone 5mg immediate release tablet, many of quality control tests must be performed to show if this products are within pharmacopeia specification, with lowest undesirable effect, better quality and better efficacy when the dose reaching the patients. Prednisolone is widely used drug for this reason testing its quality is important to guarantee safe drugs are available for patients.

1.3 Objective

1.3.1 General objective

To apply the different quality control tests for three different brands two are local and one is innovator and compared with standard.

1.3.2 Specific objective

I. To test the brands samples of prednisolone by weight variation test.
II. To measure the % loss of weight for the three brands sample of prednisolone by friability test.
III. To apply the disintegration test for the three brands.
IV. To perform the dissolution test for the three brands and find out the % of drug release.
V. To know the assay content or content uniformity of prednisolone for each brand sample.

1.4 Literature review

In (2011) a dissolution enhancement of prednisolone study was conducted by using solid dispersion technique, which was prepared with different excipients (PEG6000, dextran or lactulose). Fourier-transform infrared spectroscopy and x-ray powder diffractometer methods were employed in this study. The dissolution medium used was distilled water. The results indicated that lactose is suitable carrier to enhance the in vitro dissolution rate of prednisolone [13].

Deepak Malhotra et al, describes in there study a simple, accurate, reproducible and precise UV Spectrophotometric method for the simultaneous estimation of Azithromycin and Prednisolone in Phosphate buffer solution (pH 6.8). The absorbance maximum for Azithromycin and Prednisolone were found to be 298.6nm and 245nm, respectively. The method was validated for different parameters such as sandell's sensitivity, molar absorptivity, accuracy, precision, ruggedness, robustness, detection limit, quantification limit as per the ICH guidelines. The relative standard deviation (RSD) in case of accuracy, precision, ruggedness and robustness was less than 2.0% proving that method was highly accurate, precise and robust. This method can be used for the determination of Azithromycin and Prednisolone in pharmaceutical formulations without interference from the excipients. [14].

G. E. Francisico and others, performed in vitro and in vivo bioequivalence study of five brands of commercial prednisolone tablets. The in vivo study utilized 18 healthy males, each of whom was administered 20mg of prednisone as a reference solution or as a tablet, the blood was collected and serum was assayed using an HPLC procedure specific for prednisone and prednisolone. Mean pharmacokinetic parameters ($t_{1/2}$, k_e, C_{max}, t_{max} and AUC) were determined. The dissolution test used in the in vitro study was a standard USP dissolution test which included tablets from the same lots as the tablets used in the in vivo study. The data showed no statistical difference in any of the pharmacokinetic parameters among tableted products, subjects, or dosing periods in the study. There was also no statistical difference in the dissolution study among the five commercial tablet forms. [15].

Bagyalakshmi J at al, published there paper in International Journal of Comprehensive Pharmacy, investigating new therapeutic strategies in the treatment of inflammatory bowel disease. The objective of this study was to microencapsulate the anti-inflammatory drug (prednisolone) to provide controlled release and colon targeting. Alginate beads of prednisolone were formulated by iono-tropic gelation and further coated with Eudragit S-100 and the variables studied includes concentration of sodium alginate, different cross linking agents were evaluated with respect to particle size, surface characteristics entrapment efficiency and in vitro release behaviour. IR spectroscopic study confirmed the absence of any drug-excipient interaction. The kinetic modelling of the release data indicates that prednisolone released from alginate beads followed Korsemeyer's model. The above observations suggest that prednisolone can be developed as colon targeting drug delivery system with sodium alginate 2.5% using calcium chloride as cross linking agent and coated with Eudragit S-100. [16].

A journal of Chilean chemical society had published a paper of an accelerated chemical stability study of Prednisone oral suspension. A stability indicating chromatographic method was developed and validated according to the ICH guidelines by reversed phase using a Chromolith® C-18e monolithic column 4.6 x 100 mm, water: tetra-hydro-furan: methanol 73:23:4 v/v/v as mobile phase, UV detection at 243 nm and 1 mL/min flow rate. Prednisone drug substance was subjected to forced degradation by acid and basic hydrolysis and oxidation condition, UV-Vis radiation, temperature and relative humidity were studied to demonstrate the indicating capability of the chromatographic method. Two and five degradation products were detected upon applying acid and basic forced degradation, respectively. No degradation products were detected at the others investigated conditions. In this study, one degradation product from Prednisone oral suspension was detected during the accelerated chemical stability study. The proposed method was adequate to determine Prednisone drug substance, Prednisone oral suspension and their degradation products. [17].

2. Materials, instruments, and methods

2.1 Materials

2.1.1 Samples

Table 2.1 below show samples used in the study

Brands no.	Brand name	Manufacturer	Batch no.	Exp. date	Country of origin
A	Yesolone 5mg	Shengihi-Sudan Pharmaceutical.	180501	5/2021	Sudan
B	Cimapresone 5mg	Cima-Sudan.	180573	9/2020	Sudan
C	Hostacortin H 5mg	Sanofi (Multinational Pharmaceutical Company)	8EG007	2/2021	France.

2.1.2 Prednisolone STD

Pure API 100.5%, from shengihi-sudan pharmaceutical (Batch no: X2 190102 A), Expiry date (1/2024).

2.2 Instruments

Table 2.2 below show the instruments used in this study

i.	Analytic balance. ,(pine Brook, USA)
ii.	pH meter. (Microprocessor pH meter , HANNA instruments)
iii.	Sonicator. (BANDELIN SONOREX Typ: RK 100, Germany)
iv.	Friability tester. Type: FR1000 – Cop, (Copley, Scientific, serial No: 12945).
v.	Disintegration Tester. Type: NE4 – Cop, (Copley, Scientific, serial No: 13012).
vi.	Dissolution Tester. Type: NE4 – Cop, (Copley, Scientific, serial No: 13010).
vii.	UV-Visible Spectrophotometer. No (1800), (Shimadzu-Japan).
viii.	High Performance Liquid Chromatography (HPLC). (Shimadzu).

2.3 Methods

2.3.1 Weight Variation test

(According to British Pharmacopeia (BP) (2012) standards. [18])

Twenty tablets of each brand were selected randomly. Each tablet was weighed individually and then all the twenty tablets were weighed as whole. Weight variation was calculated by dividing the summation of each tablet over the whole twenty tablets. Then standard deviation and standard error were calculated.

2.3.2 Friability test

(According to British Pharmacopeia (BP) (2012) standards. [18])

Twenty tablets of each brand were weighed, and then any brand alone was subjected to abrasion and shock condition on friabilator at 25rpm for 4 minutes. After that they were weighed again for calculation of the percentage loss of weight.

2.3.3 Disintegration test

(According to British Pharmacopeia (BP) (2012) standards. [18])

Six tablets of each brand were placed in disintegration apparatus by using distilled water as disintegration medium. The apparatus was operated under 37^{o}C. The time at which all tablets were completely disintegrated was reported.

2.3.4 Dissolution test

(Release rate of Prednisolone tablet is carried on according to the general procedure of United States Pharmacopoeia (USP) [19]).

2.3.4.1 The condition

Table 2.3 below show the condition at which the dissolution test was performed

Apparatus	USP 2 Paddle
Dissolution medium	900ml pH 7, Distilled water
Temperature	37°C (±0.5)
Stirring Speed	50rpm
Time	30 minutes

2.3.4.2 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). Tablets of Prednisolone were transferred to each six vessels. The apparatus was started to operate at 50 rpm. At the end of 1st hour, 10ml samples were withdrawn from each vessel and filtered through 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.

The amount of drug present in the samples was calculated with the help of straight-line equation obtained from the calibration curve of Prednisolone standard.

2.3.4.2 Preparation of Standard Solution

Exactly 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 was put in the sonicator for 5 minutes and made up to the mark. From the above solution 10ml was taken in another clean and dry 100ml volumetric flask and 50ml distilled water was added to make the solution. The solution was put in sonicator for 5minutes and the volume was adjusted to make up the mark. Concentrations of 1ppm, 2ppm, 3ppm, 4ppm and 5ppm were prepared in five, (25ml volumetric flask).

2.3.5 Assay of Prednisolone by HPLC

(According to United States Pharmacopoeia (USP) [20].)

Twenty tablets of each brand were weighed and powdered by mortar & pestle, quantity that contain 5mg of Prednisolone was taken and added 58ml of methanol, shaken for 10 min, sufficient water was added to produce 100ml, and then was mixed and filtered. The filtrated solution was taken and read by HPLC.

Procedure carried out using the following condition in table 2.4 below

Column	20cm*4.6mm.
Stationary phase	(5micrometer) (spherisorb ODS 1 is suitable).
Mobile phase	Mixture of 42ml of water & 58ml of methanol.
Flow rate	1ml per minute.
Detection wavelength	254 nm.

3. Results

3.1 weight variation tests

3.1.1 Brand (A), (Yesolone)

Table 3.1 show the weight variation test results for brand (A)

No of tablet	Weight(gm) (X)	(x-μ)	(x-μ)^2
1	0.0809	0.0003	0.0009×10^{-4}
2	0.0802	0.0004	0.0016×10^{-4}
3	0.0807	0.0001	0.0001×10^{-4}
4	0.0789	0.0017	0.0289×10^{-4}
5	0.0808	0.0002	0.0004×10^{-4}
6	0.0797	0.0009	0.0081×10^{-4}
7	0.0793	0.0013	0.0169×10^{-4}
8	0.0812	0.0006	0.0036×10^{-4}
9	0.0819	0.0013	0.0169×10^{-4}
10	0.0815	0.0009	0.0081×10^{-4}
11	0.0807	0.0001	0.0001×10^{-4}
12	0.0794	0.0012	0.0144×10^{-4}
13	0.0823	0.0017	0.0289×10^{-4}
14	0.0813	0.0007	0.0049×10^{-4}
15	0.0810	0.0004	0.0016×10^{-4}
16	0.0811	0.0005	0.0025×10^{-4}
17	0.0807	0.0001	0.0001×10^{-4}
18	0.0801	0.0005	0.0025×10^{-4}
19	0.0815	0.0009	0.0001×10^{-4}
20	0.0805	0.0001	0.0001×10^{-4}
Total	$\sum(x) = 1.6137$	none	$\sum(x-\mu)^2 = 0.1487\times10^{-4}$
	Mean (μ) = 0.0807	Standard deviation (SD) = 0.0009	Relative Standard deviation (RSD) = 1.1%

3.1.2 Brand (B), (Cimapresone)

Table 3.2 show the weight variation test results for brand (B)

No of tablet	Weight(gm) (X)	(x-μ)	(x-μ)^2
1	0.1015	0.00052	0.0027×10^{-6}
2	0.1015	0.00052	0.0027×10^{-6}
3	0.1011	0.00012	0.0001×10^{-6}
4	0.1014	0.00042	0.0017×10^{-6}
5	0.1017	0.00072	0.0051×10^{-6}
6	0.1004	0.00058	0.0033×10^{-6}
7	0.1022	0.00122	0.0148×10^{-6}
8	0.1009	0.00008	0.0001×10^{-6}
9	0.1004	0.00058	0.0033×10^{-6}
10	0.0992	0.00178	0.0316×10^{-6}
11	0.1008	0.00018	0.0003×10^{-6}
12	0.1012	0.00022	0.0004×10^{-6}
13	0.0994	0.00158	0.0249×10^{-6}
14	0.1006	0.00038	0.0014×10^{-6}
15	0.1008	0.00018	0.0003×10^{-6}
16	0.1006	0.00038	0.0014×10^{-6}
17	0.1018	0.00082	0.0067×10^{-6}
18	0.1014	0.00042	0.0017×10^{-6}
19	0.1005	0.00048	0.0023×10^{-6}
20	0.1022	0.00122	0.0148×10^{-6}
Total	$\sum(x) = 2.0196$	none	$\sum(x-\mu)^2 = 0.1234\times10^{-6}$
	Mean (μ) = 0.1009	Standard deviation (SD) = 0.0001	Relative Standard deviation (RSD) = 0.1%

3.1.3 Brand (C) , (Hostacortin H)

Table 3.3 show the weight variation test results for brand (C)

No of tablet	Weight(gm) (X)	(x-μ)	$(x-\mu)^2$
1	0.1036	0.00206	0.0424×10^{-6}
2	0.1017	0.00016	0.0002×10^{-6}
3	0.1016	0.00006	0.00004×10^{-5}
4	0.1018	0.00026	0.0006×10^{-6}
5	0.1017	0.00016	0.0002×10^{-6}
6	0.1014	0.00014	0.0001×10^{-6}
7	0.1027	0.00116	0.0134×10^{-6}
8	0.1015	0.00004	0.00002×10^{-5}
9	0.1023	0.00076	0.0057×10^{-6}
10	0.1023	0.00076	0.0057×10^{-6}
11	0.1000	0.00154	0.0237×10^{-6}
12	0.1016	0.00006	0.00004×10^{-5}
13	0.1030	0.00146	0.0213×10^{-6}
14	0.0991	0.00244	0.0595×10^{-6}
15	0.1016	0.00006	0.00004×10^{-5}
16	0.1008	0.00074	0.0054×10^{-6}
17	0.1010	0.00054	0.0029×10^{-6}
18	0.1013	0.00024	0.0005×10^{-6}
19	0.1002	0.00134	0.0179×10^{-6}
20	0.1016	0.00006	0.00004×10^{-5}
Total	$\sum(x) = 2.0308$	none	$\sum(x-\mu)^2 = 0.1947\times10^{-6}$
	Mean (μ) =0.1015	Standard deviation (SD) = 0.0001	Relative Standard deviation (RSD) = 0.1%

3.2 Friability tests

The results were recorded in the table 3.4 below

brand No	Weight before test	Weight after test	% of remaining	% of lost	Comment
A	1.8074	1.8067	99.96	0.04	Passed
B	1.9975	1.9865	99.45	0.55	Passed
C	1.5954	1.5949	99.97	0.03	Passed

3.3 disintegration tests

The time at which all tablets in the instrument were disintegrated on the distilled water (37℃) are recorded in the table 3.5 below

brand No	Disintegration time(sec)	comment
A	87 sec (6:27 min)	Passed
B	7 sec	Passed
C	18 sec	Passed

3.4 Dissolution tests

3.4.1 Standard calibration curve

Table 3.6 below shows the concentrations of (STD) that were prepared and it's absorbance in U.V spectrophotometric instrument

Concentration (ppm)	Absorbance at (246nm)
1	0.057
2	0.091
3	0.139
4	0.190
5	0.231

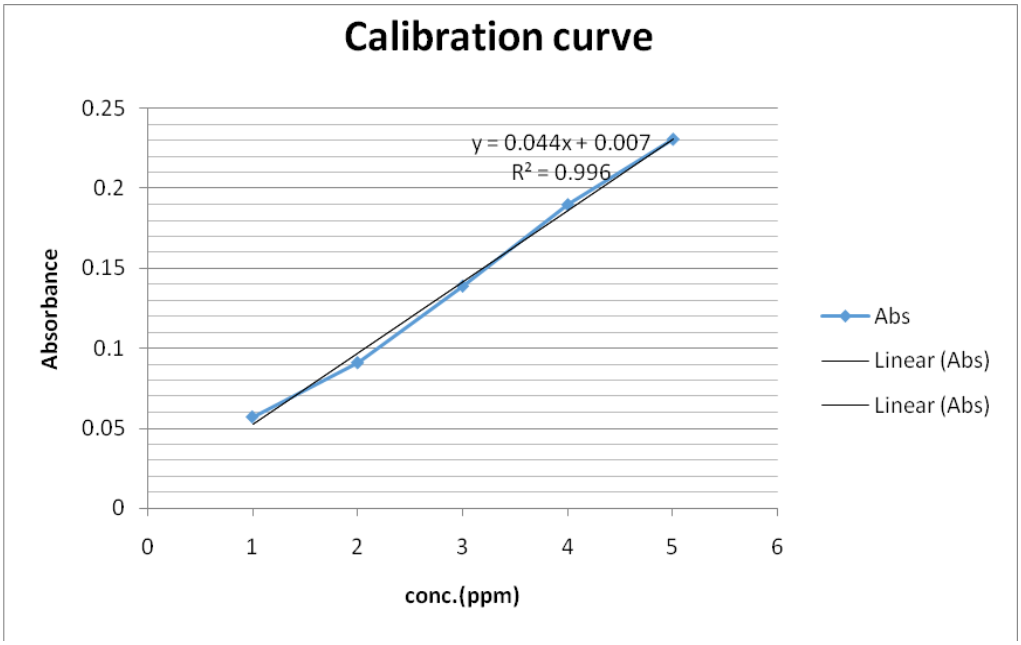

Figure 3.1 below show the calibration curve of the prednisolone STD

3.4.2 Dissolution test results

There was a problem with the dissolution tester .

3.5 Assay by HPLC

The chromatograms illustrated by HPLC for the STD and the three brands sample, and the % contents of Prednisolone was found for each brand sample

3.5.1 Standard (STD) of Prednisolone

Sharp and symmetrical peak was obtained at 4:22min with peak area of 2752877 and concentration of 200ppm.

3.5.2 Brand (A), (yesolone)

Sharp and symmetrical peak was obtained at 4:24min with peak area of 2350513 and concentration of 170.76ppm.

3.5.3 Brand (B), (Cimapresone)

Sharp and symmetrical peak was obtained at 4:25min with peak area of 2343988 and concentration of 170.29ppm.

3.5.4 Brand (C), (Hostacortin H)

Sharp and symmetrical peak was obtained at 4:26 min with peak area of 2322316 and concentration of 168.71ppm.

3.5.5 Result of the three brands

Table 3.8 below show the results of assay test

Brand	Assay	Amount of Prednisolone
A	**85.38%**	**4.27mg**
B	**85.15%**	**4.26mg**
C	**84.36%**	**4.22mg**

4. Discussion, conclusion and recommendations

4.1 Discussion and conclusion

The results obtained from the tests that were performed for the three brands in this study are discussed below:

4.1.1 Weight variation

British Pharmacopeia for the weight variation stated that the tablets containing 80mg or less of the active ingredient like my samples here in these study (5mg of Prednisolone), must not be more than two tablets deviates from the mean by ±10%. The relative standard deviation (RSD) and STD deviation (SD) of brands (A), (B) and (C) were found to be [(RSD) = 1.1%, (SD) = 0.0009], [(RSD) = 0.1%, (SD) = 0.0001] and [(RSD) = 0.1%, (SD) = 0.0001] respectively. All samples were within the specification

4.1.2 Friability test

British Pharmacopeia for the friability test stated that the % loss of weight for all twenty tablets must not be more than 1%. The % loss of weight for the three brands (A), (B) and (C) were found to be [0.04], [0.55] and [0.03] respectively. All the brands samples passed the test.

4.1.3 Disintegration test

British Pharmacopeia for the disintegration test stated that: the disintegration time of uncoated tablet must not be more than 15 minute. The disintegration time of brands (A), (B) and (C) were found to be [6:27min], [7sec] and [18sec] respectively. All the brands passed the test.

4.1.4 Assay by HPLC

According to USP monographs HPLC assay should be within 90%-110%. The % content of Prednisolone in brands (A), (B) and (C) were found to be [85.38%], [85.15%] and [84.36%] respectively. All brands samples fail in this test, which it's the critical one of all the tests performed.

Table 4.1 below show comparative summary of tests for the brands

Test name	Brand (A)	Brand (B)	Brand (C)
Weight variation	Passed	Passed	Passed
Friability	Passed	Passed	Passed
Disintegration Assay	Passed Failed	Passed Failed	Passed Failed

4.2 Recommendations

- Periodic quality control tests are better to be performed by manufacturer for the API content, finished products in the quarantine and finished products in markets by recalls of some samples from markets.
- Receiving and dispatch places should be separated and protect materials and products from the weather.
- Accelerated stability study must be performed in order to determine the optimal storage conditions.
- In the manufacturer area electrical supply, lighting, temperature, humidity and ventilation should be appropriate and do not adversely affect, either the pharmaceutical products or the accurate functioning of equipment's.
- More samples must be analyzed.
- More brands must be analyzed.

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