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Research Paper

Comparative Dissolution Study of Levofloxacin Tablets

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ABSTRACT: *Levofloxacin is a broad-spectrum antibiotic and functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV (an enzyme which is inhibiting cell division by separating replicated DNA). In 1996, Levofloxacin was approved for medical use in the United States. Dissolution studies can serve several purposes as, for example, to be used as a tool in quality control to demonstrate consistency in manufacture, to demonstrate similarity between reference products from different Member States, to demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product. The purpose of this study was to determine the percent of Levofloxacin dissolved from Tablets at 15, 30, 45, 60 and 120 minutes in the conditions assessed by in vitro dissolution test in three dissolution media with purified water. The simiarity factor's value, f_2, calculated with the obtained results using as dissolution medium water was 80.94. Because the simiarity factor's value was situated between 50 and 100, the two dissolution profiles are similar.*

Keywords: *Levofloxacin, Dissolution, Simiarity factor's.*

I. INTRODUCTION

Levofloxacin is a quinolone antimicrobial agent and it acts as a broad-spectrum antibiotic against gram-positive and gramnegative aerobes[1]. It is the L-isomer of the racemate ofloxacin. Chemical name of Levofloxacin is 9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, hemihydrates[2]. Levofloxacin is the most important medications needed in a basic health system and World Health Organization is listed it as Essential Medicine. Levofloxacin is used to treat the different types of bacterial infections including pneumonia, urinary tract infections, acute bacterial sinusitis, chronic prostatitis. Combination with other antibiotics it may be used to treat tuberculosis, meningitis or pelvic inflammatory disease. It is administered by both oral route and intravenous route[3]. Levofloxacin is a light-yellowish-white to yellow-white crystal or crystalline powder and the molecular weight is 370.38[4]. It is freely soluble in acidic aqueous solutions but relatively insoluble in water[5].

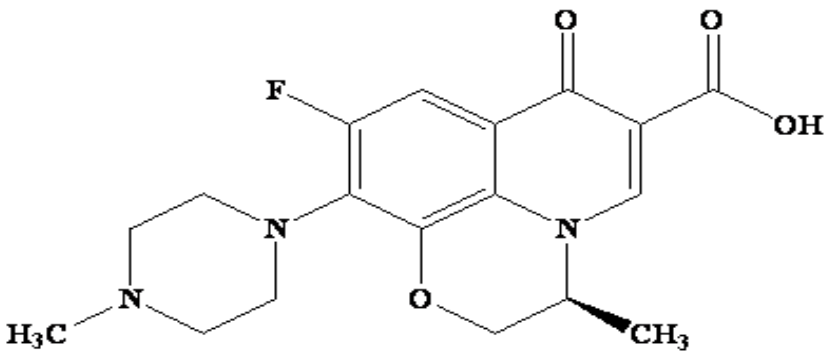

Figure 1: Levofloxacin[5]

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The purpose of the *in-vitro* dissolution studies in the early stage of drug development is to select the optimum formulation, evaluate the active ingredient and excipient, and assess any minor changes for drug products[6]. However, for the IVIVC perspective, dissolution is proposed to be a surrogate of drug bioavailability. Thus, a more rigorous dissolution standard may be necessary for the *in-vivo* waiver[7]. Generally, a dissolution methodology, which is able to discriminate between the study formulations and which best, reflects the *in vivo* behavior would be selected [6]. USP & NF recognized seven dissolution apparatus specifically and describes with allowable modifications in detail. The choice should be considered during the development of the dissolution methods, since it can affect the results and duration of the test. The type of dosage form under investigation is the primary consideration in apparatus selection. The compendial apparatus for dissolution as per USP are: Apparatus 1 (rotating basket), Apparatus 2 (paddle assembly), Apparatus 3 (reciprocating cylinder), Apparatus 4 (flow-through cell), Apparatus 5 (paddle over disk), Apparatus 6 (cylinder), Apparatus 7 (reciprocating holder). The European Pharmacopoeia has also adopted some of the apparatus designs described in the USP, with some minor modifications in the specifications[8].

II. MATERIALS AND METHODS

2.1 Levofloxacin 500 mg Tablet(manufactured in research laboratory) and Trevox 500 mg Tablet (manufactured by Square Pharmaceuticals Ltd.) was used as a test sample and reference sample respectively.

2.2 Dissolution conditions:

- apparatus-2 (Paddle type);
- Volume of dissolution medium: 900 ml;
- Rotation speed: 50 rpm;
- Dissolution medium teperature: 37.0 ± 0.5 ^{0}C;
- Sampling time: 15, 30, 45, 60, 120 minute.
- Dissolution medium: Purified Water

(i) Standard solution preparation:

50 mg Levofloxacin was quantitatively transferred into a 100 ml volumetric flask was added dissolution medium and volume up to 100 ml with dissolution medium. Take 2 ml from this solution in a 100 ml volumetric flask and volume up to 100 ml with dissolution medium.

(ii) Sample solutions preparation

Approximately 20 ml sample solution was taken from each dissolution tester vessel & filtered this solution through Whiteman filter paper (0.45µ). 2 ml of filtrate was taken in a 100 ml volumetric flask and volume up to 100 ml with dissolution medium. The absorbance for sample solutions and standard solutions were measured at 290 nm, using the dissolution medium for control.

The percent of dissolved Levofloxacin was calculated with the following formula:

$$C_t = \frac{A_p \times m_e}{A_e} \quad \text{(Formula 1)}$$

where:

A_p = absorbance of the sample solution;

A_e = absorbance of the standard solution;

m_e = Levofloxacin s.r. weight mass used to prepare the standard solution, mg;

For calculate the percent of dissolved Levofloxacin at 15,30, 45, 60 and 120 minutes was made a correction using the following calculation formula:

$$Q_t = [C_t \times (1 - t\frac{10}{900})] + [\frac{10}{900}\sum_{n=2}^{n=t} C_{(n-1)}] \quad \text{(Formula 2)}$$

where:

t = a coefficient which may be equal to 1 for the samples taken at 15 minutes, 2 for the samples taken at 30 minutes and 3 for the samples taken at 45 minutes,4 for the samples taken at 60 minutes,5 for the samples taken at 120 minutes

10 = the volume of sample taken;

900 = the volume of dissolution medium;

C_t = the percent of dissolved Levofloxacin, calculate with formula 1.

To evaluate the similarity of dissolution profiles for the test product and the reference product was necessary to calculate the similarity factor f_2.

The similarity factor was calculated with the following formula:

$$f_2 = 50 * \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n} [\bar{R}(t) - \bar{T}(t)]^2}{n}}} \right] \quad \text{(Formula 3)}$$

where:

n = the number of points corresponding to time range at which was determined the dissolved content;

R(t) = the average value of dissolved percent at the *t* time moment of the reference product;

T(t) = the average value of dissolved percent at the *t* time moment of the test product.

Two dissolution profiles are considered similar when the value of similarity factor (f_2) is ≥ 50.

III. RESULTS

In comparative dissolution study, the method was used only for finished product where water was used as medium. Levofloxacin 500 mg Tablet and Trevox 500 mg Tablet (manufactured by Square Pharmaceuticals Ltd.) was used as a test sample and reference sample respectively.

Table 1: Results of dissolution of test sample and reference sample in water

	0 Minutes		15 Minutes		30 Minutes		45 Minutes		60 Minutes		120 Minutes	
	G	P	G	P	G	P	G	P	G	P	G	P
% of disso-lution	0	0	70.31	73.45	85.18	88.88	93.28	94.25	96.2	95.99	98.99	99
	0	0	69.78	72.90	84.54	88.21	92.58	93.54	96.19	95.27	98.25	98.26
	0	0	69.61	72.72	84.33	87.99	92.35	93.31	95.24	95.03	98.00	98.01
	0	0	70.91	74.07	85.90	89.64	94.07	95.05	97.02	96.81	99.83	99.84
	0	0	70.06	73.35	84.88	88.21	93.19	94.20	96.83	95.27	98.25	98.26
	0	0	69.27	72.36	83.92	87.97	92.53	92.86	96.18	94.57	97.52	97.53
	0	0	70.84	74.00	85.82	89.55	93.98	94.10	96.92	96.71	99.73	98.84
	0	0	70.24	73.09	84.81	88.44	92.85	93.82	96.43	95.55	98.53	98.54
	0	0	69.99	73.13	84.88	88.20	92.57	91.65	97.03	95.26	98.24	98.87
	0	0	71.00	74.17	86.01	89.75	94.19	93.84	97.14	96.93	99.96	99.97
	0	0	71.01	74.18	86.03	89.77	94.21	93.85	97.16	96.95	99.98	98.98
	0	0	70.91	74.07	85.90	89.64	94.07	93.92	97.02	96.81	99.83	98.58
Average	0	0	70.33	73.46	85.18	88.85	93.32	93.70	96.61	95.93	98.93	98.72
SD	0	0	0.576	0.606	0.702	0.723	0.710	0.804	0.554	0.832	0.858	0.670

Where,

G = Values for test product (Generic)

P = Values for reference product (Pioneer)

SD = Standard Deviation

Calculation of similarity factor (f_2):

Table 2: Results of dissolution of test sample and reference sample in water

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}{}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

Time	RT	T_t	R_t-T_t	SR.R_t-T_t
15	73.46	70.33	3.13	9.80
30	88.85	85.18	3.67	13.47
45	93.70	93.32	0.38	0.14
60	95.93	96.61	-0.68	0.47
120	98.72	98.93	-0.20	0.04
Sum	450.66	444.37	6.29	23.92
Sum/n	5			4.7842
Add 1	1			5.7842
SQRT				2.4050
1/n				0.4158
*100				41.5793
Log				1.6189
*50	**Similarity factor(** f2)			80.9439

Where,
f_2= Similarity factor
n= Number of units taken
R_t= Cumulative percentage of dissolution for the reference sample
T_t= Cumulative percentage of dissolution for the test sample
QRT= Square Root of Test Sample value.
Sum=Average value.

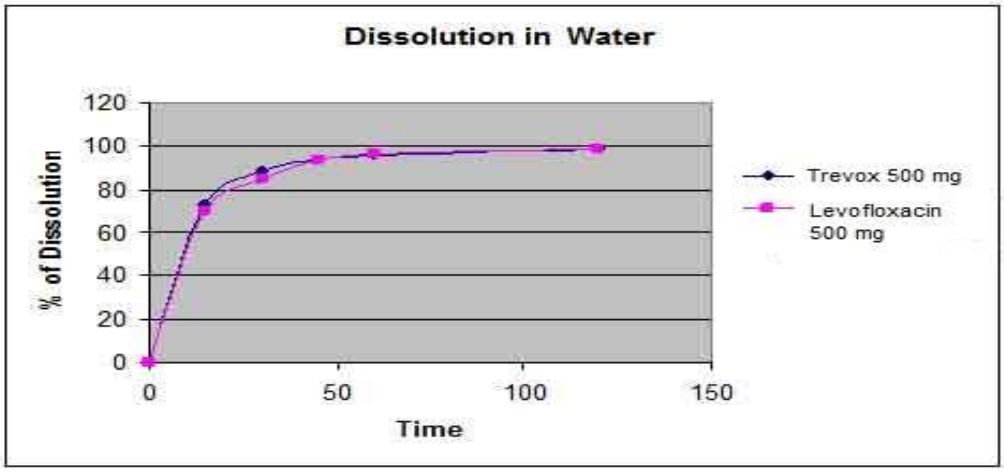

Figure 2: Graph of % of dissolution against time for test and reference sample in water

IV. DISCUSSION

All solid oral dosage forms are undergoing Dissolution testing. Dissolution testing is used for all phases of development for product release and stability testing [9]. Release of drug from formulations is understood by *in vitro* dissolution testing. It has also been employed as a quality control (QC) procedure, in R&D to detect the influence of critical manufacturing variables [10]. In this study,The active substance and strength of Levofloxacin 500 mg Tablet are the same with that of Trevox 500 mg Tablet; the pharmaceutical form is the same, Tablet.Considering the fact that obtained values for the simiarity factor (f_2) in each of the dissolution media are ranged between 50 and 100, *in vitro* dissolution profiles for the products Levofloxacin 500 mg TABLET and Trevox 500 mg TABLET, Batch 0120235E1212, manufactured by Square Pharmaceuticals Ltd.

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