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FORMULATION AND COMPARATIVE DISSOLUTION STUDY OF LEFLUNOMIDE FILM COATED TABLETS WITH A REFERENCE PRODUCT

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ABSTRACT

The main objective of the present study is to conduct the comparative dissolution study of a generic brand of same strength and dosage form and treatment of obtained dissolution data by using similarity factor ($f2$) to determine whether the formulations used were equivalent or significantly different. Leflunomide is a class II drug as per BCS (Biopharmaceutical Classification System) which means it has a low aqueous solubility and high permeability. It is of utmost importance to understand the release profiles of such drugs to relate with the *in vivo* availability. Hence, the study was developed to compare the *in vitro* dissolution profiles of Leflunomide film coated tablets (Lef-20) with a Reference product available in Nepalese market (Lefra- 20) by applying bio-relevant medium (pH 1.2, 4.5 and 6.8 buffers). *In vitro* dissolution profiles were evaluated in bio-relevant medium in dissolution apparatus and the dissolution curves were compared by the similarity factor (f2). The dissolution profiles of the test and the reference products demonstrated similar disposition in all bio-relevant media. Therefore, dissolution profiles in bio-relevant media in dissolution apparatus may be used as a tool to predict and correlate *in vivo* disposition of formulations of Leflunomide tablets. Furthermore, it can be argued that bio-waiver can be granted for film coated formulations of Leflunomide on the basis of *in vitro* dissolution profile.

KEYWORDS: Leflunomide, film coated tablets, similarity factor, BCS, dissolution profile.

1. INTRODUCTION

Leflunomide is an isoxazole derivative and inhibitor of *de novo* pyrimidine synthesis, which has been shown to provide comparable suppression of joint inflammation to methotrexate and sulphasalazine, thereby reducing the rate of radiologically detected joint damage and reversing disability.[1]

Leflunomide is an immunomodulatory oral medication that becomes metabolized in the body to its active form metabolite *A77-1726*, also known as teriflunomide. This metabolite acts by inhibiting the mitochondrial enzyme dihydro-orotate dehydrogenase. This action prevents the synthesis of ribonucleotide uridine monophosphate pyrimidine (rUMP) and decreases rUMP levels, further activating P53. The activation of P53 restricts the progression of the G1 to S-phase in the cell cycle. This restriction halts the proliferation of activated and autoimmune lymphocytes promoting anti-inflammatory and immunomodulatory effects.[2,3,4]

Out of the many routes of administration available, the oral route remains the most popular dosage form among patients as it is easy to use and carry around and causes minimal discomfort for many patients.[5] When the oral drug is swallowed, first dissolution of the drug *in vivo* occurs to produce a solution and then the dissolved drug is transported across the gastrointestinal membrane.[6] Therefore, among the many factors that affect bioavailability of any drug, one of the most important factors is gastrointestinal (GI) dissolution and permeability especially for low water soluble drugs which will be released slowly in the gastrointestinal tract.[7] If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of drug becomes the rate-limiting step in the absorption process.[8] This is manifested in case of class II drugs in the Biopharmaceutics Classification System (BCS) which are hydrophobic, poorly soluble, and highly permeable and readily absorbed drugs and class IV drugs which are of low solubility and low permeability.[9]

Leflunomide is a BCS Class-II drug with low aqueous solubility and high permeability which requires a bioequivalence study to correlate with *in vivo* availability. Therefore, in this research, a comparative study of *in vitro* dissolution profiles of test product (Lef-20) and a reference product was carried out to confirm their similarity in release pattern.

Leflunomide is a monocarboxylic acid amide obtained by formal condensation of the carboxy group of 5-methyl-1, 2-oxazole-4-carboxylic acid with the anilino group of 4-

(trifluoromethyl) aniline. Its IUPAC name is 5-methyl-*N*-[4-(trifluoromethyl) phenyl]-1, 2-oxazole-4-carboxamide. The chemical structure of the drug is shown in Figure 1.

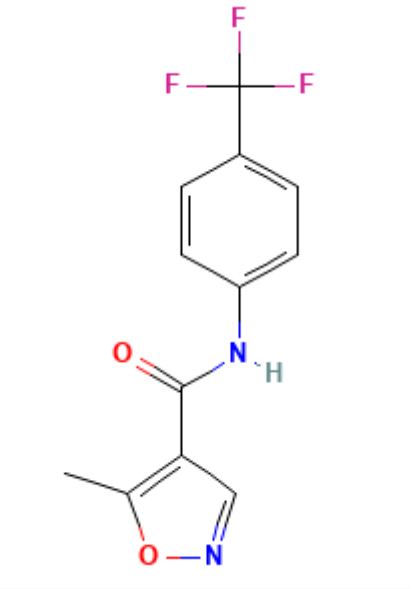

Figure 1: Chemical structure of Leflunomide.[10]

2. MATERIALS AND METHODS

2.1 MATERIALS

The pure leflunomide raw material was received from Cipla Ltd, Mumbai, India. Other excipients used during formulation of test product were starch, lactose monohydrate, Croscarmellose sodium, PVPK-30, Purified talc, and Magnesium Stearate. Similarly, ethyl cellulose was used as a film coating agent.

2.2 METHODS

2.2.1 Dissolution Test

In Medium I

Apparatus used: Dissolution Test Apparatus Type I (Paddle)

Medium: 1000ml of 1.2pH HCl

Speed and Time: 75 rpm and 30 minutes

In Medium II

Apparatus: Dissolution Test Apparatus Type I (Paddle)

Medium: 1000ml of pH 4.5

Speed and Time: 75 rpm and 30 minutes

In medium III

Apparatus: Dissolution Test Apparatus Type I (Paddle)

Medium: 1000ml of pH 6.8 buffer

Speed and Time: 75 rpm and 60 minutes

1000 ml of required buffer was introduced as dissolution medium into the vessel of apparatus. The dissolution medium was warmed to 36.5°C- 37.5°C. One tablet was placed in each vessel and run the apparatus for designated time.

A suitable volume of the medium was withdrawn and filtered. The absorbance of the filtered solution was measured immediately, suitably diluted with the dissolution medium, if necessary, at the maximum at about 262nm. The content of Leflunomide in the medium was calculated from the absorbance obtained from a solution of known concentration of leflunomide Reference Standard (RS) prepared by dissolving in minimum quantity of methanol and diluted with the dissolution medium.

The absorbance of sample and standard was measured at 262nm and calculated as:

$$\%\ Release = \frac{Abrobance\ of\ test}{Absorbance\ of\ standard} x \frac{weight\ of\ standard\ (mg)}{Standard\ dilution} x \frac{Sample\ dilution}{Label\ claim} x \frac{Potency}{100} x100$$

2.2.2 SIMILARITY FACTOR

The similarity factor (f2) is a logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R-T)^2]^{-0.5} \times 100$$

Where n is the number of time points, R is the dissolution value of the reference (prechange) batch at time t, and T is the dissolution value of the test (postchange) batch at time t.

Experimental data were analyzed through an independent approach using the similarity factor (f2) to compare the dissolution profiles. Curves were considered similar if f2 values were between 50 and 100.

3. RESULTS AND DISCUSSION

3.1 MEDIUM I (pH 1.2 HCl)

3.1.1 Test Product Dissolution Data in Medium-I

Table 1: Cumulative percentage drug released (test) in pH 1.2 HCl.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (TEST PRODUCT: LEF 20)		
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)
1	64.454	70.754	75.274
2	57.453	70.109	73.538
3	57.822	69.773	73.449
4	61.024	70.149	77.393
5	61.761	70.667	74.479
6	64.426	71.774	78.176
7	64.539	70.868	75.247
8	57.425	70.137	73.510
9	57.935	69.803	73.506
10	61.110	70.235	77.394
11	61.676	70.610	74.507
12	64.511	71.832	78.262
MIN	**57.425**	**69.773**	**73.449**
MAX	**64.539**	**71.832**	**78.262**
AVERAGE	**61.178**	**70.559**	**75.395**
% RSD	**2.924**	**0.680**	**1.906**

3.1.2 Reference Product Dissolution Data in Medium-I

Table 2: Cumulative percentage drug released (Reference) in pH 1.2 HCl.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (REFERENCE PRODUCT: LEFRA-20)		
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)
1	60.649	75.642	86.992
2	62.898	78.448	80.929
3	58.726	73.816	82.475
4	61.833	78.052	85.865
5	60.620	75.228	84.591
6	61.389	78.491	86.373
7	59.880	75.604	87.287
8	61.418	78.550	81.226
9	59.022	74.115	82.537
10	60.975	75.084	85.980
11	60.472	75.404	84.741
12	60.294	78.390	86.431
MIN	**58.726**	**73.816**	**80.929**
MAX	**62.898**	**78.550**	**86.992**
AVERAGE	**60.681**	**76.402**	**84.619**
% RSD	**1.159**	**1.836**	**2.268**

Similarity Factor (f2 calculation): 62.76

Graphical representation

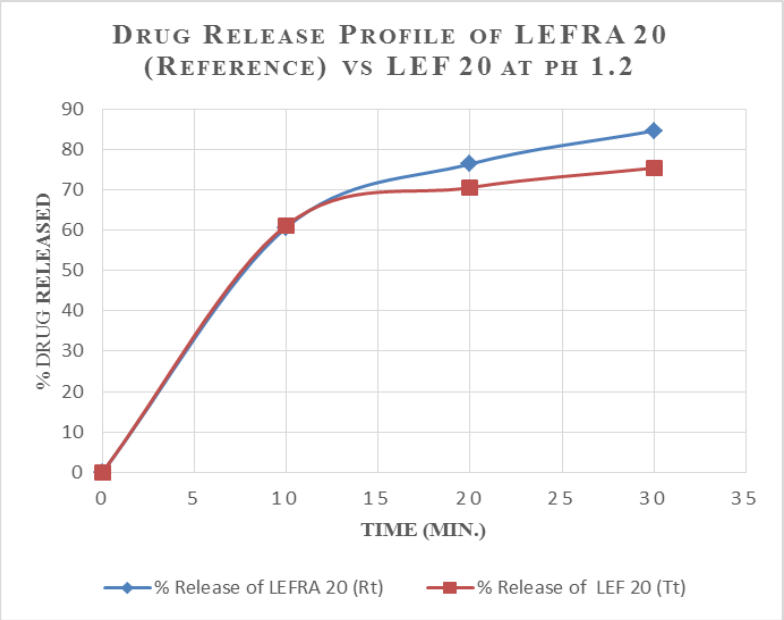

Figure 2: Drug release profile of Reference Product (Lefra-20) vs. Test (Lef-20) at pH 1.2.

Figure 2 demonstrates that the similarity factor of drug release profile of reference vs. test product at pH 1.2 is 62.76 showing similar pattern of release.

3.2 Medium II (pH 4.5 buffer)

3.2.1 Test Product Dissolution Data in Medium-II

Table 3: Cumulative percentage drug released (Test Product) in pH 4.5 buffer.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (TEST PRODUCT: LEF 20)		
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)
1	70.712	75.706	79.528
2	67.151	75.342	77.199
3	68.623	77.713	82.404
4	70.153	79.407	83.483
5	65.680	75.885	77.264
6	68.034	73.498	77.473
7	70.388	75.673	79.733
8	67.387	75.492	79.202
9	68.534	77.800	82.523
10	69.329	78.810	83.329
11	65.739	75.915	77.323
12	68.328	73.413	77.560
MIN	**65.680**	**73.413**	**77.199**

MAX	**70.712**	**79.407**	**83.483**
AVERAGE	**68.338**	**76.221**	**79.752**
% RSD	**1.664**	**1.882**	**2.530**

3.2.2 Reference Product Dissolution Data in Medium-II

Table 4: Cumulative percentage drug released (Reference Product) in pH 4.5 buffer.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (REFERENCE PRODUCT: LEFRA- 20)		
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)
1	55.090	69.211	72.855
2	53.215	65.029	69.791
3	53.186	66.524	72.972
4	57.200	68.063	75.744
5	51.808	66.186	74.082
6	53.596	66.089	73.524
7	55.325	69.302	73.091
8	53.420	65.442	72.667
9	53.479	66.644	73.091
10	57.288	68.620	75.867
11	51.779	66.274	74.669
12	53.684	66.119	73.759
MIN	**51.779**	**65.029**	**69.791**
MAX	**57.288**	**69.302**	**75.867**
AVERAGE	**54.089**	**66.959**	**73.509**
% RSD	**1.804**	**1.458**	**1.592**

Similarity Factor (f2 calculation): 52.03

Graphical representation

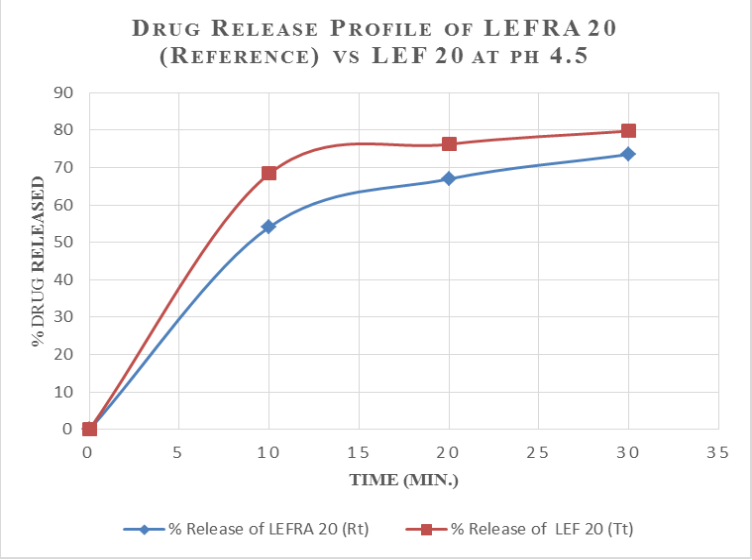

Figure 3: Drug release profile of Reference Product (Lefra-20) vs. Test (Lef-20) at pH 4.5

Figure 3 demonstrates that the similarity factor of reference vs. test products at pH 4.5 is 52.03 which show they both have acceptable and similar release patterns.

3.3 Medium III (pH 6.8 buffer)

3.3.1 Test Product Dissolution Data in Medium-III

Table 5: Cumulative percentage drug released (Test Product) in pH 6.8 buffer.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (TEST PRODUCT: LEF 20)				
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)	Time point 4 (45 min)	Time point 5 (60 min)
1	57.895	74.614	76.975	80.439	88.971
2	61.128	76.766	79.497	80.262	87.999
3	57.866	72.792	81.157	83.689	82.865
4	56.749	71.751	78.383	78.251	79.836
5	59.718	72.166	80.445	79.420	83.758
6	62.010	74.219	81.878	82.963	86.589
7	58.072	74.616	77.151	80.412	88.736
8	61.158	76.737	79.438	80.437	88.119
9	57.807	72.850	81.187	83.719	82.895
10	56.837	71.958	78.591	78.312	82.776
11	59.776	72.196	80.475	79.567	83.995
12	62.039	74.278	81.850	82.903	86.648
MIN	**56.749**	**71.751**	**76.975**	**78.251**	**79.836**
MAX	**62.039**	**76.766**	**81.878**	**83.719**	**88.971**
AVERAGE	**59.255**	**73.745**	**79.752**	**80.865**	**85.266**
% RSD	**1.962**	**1.755**	**1.701**	**1.971**	**2.954**

3.3.2 Reference Product Dissolution data in Medium -III

Table 6: Cumulative percentage drug released (Reference Product) in pH 6.8 buffer.

S. No.	CUMULATIVE PERCENTAGE DRUG RELEASED (REFERENCE PRODUCT: LEFRA 20)				
	Time point 1 (10 min)	Time point 2 (20 min)	Time point 3 (30 min)	Time point 4 (45 min)	Time point 5 (60 min)
1	45.399	67.499	75.771	78.014	79.473
2	45.923	61.051	72.086	78.442	78.623
3	50.336	66.010	72.307	77.728	80.353
4	48.074	64.936	72.626	73.870	79.014
5	48.957	65.581	72.578	76.489	82.408
6	54.611	67.684	76.352	79.703	77.479
7	45.178	67.221	75.906	78.043	79.612
8	45.812	62.374	72.266	79.823	78.914
9	51.025	66.790	72.426	77.812	80.795
10	48.240	66.869	72.923	73.928	79.842
11	49.012	65.636	73.130	77.737	83.249
12	54.363	67.930	76.438	79.925	80.543

MIN	**45.178**	**61.051**	**72.086**	**73.870**	**77.479**
MAX	**54.611**	**67.930**	**76.438**	**79.925**	**83.249**
AVERAGE	**48.911**	**65.798**	**73.734**	**77.626**	**80.025**
% RSD	**3.229**	**2.138**	**1.790**	**2.012**	**1.603**

Similarity Factor (f2 calculation): 55.18

Graphical representation

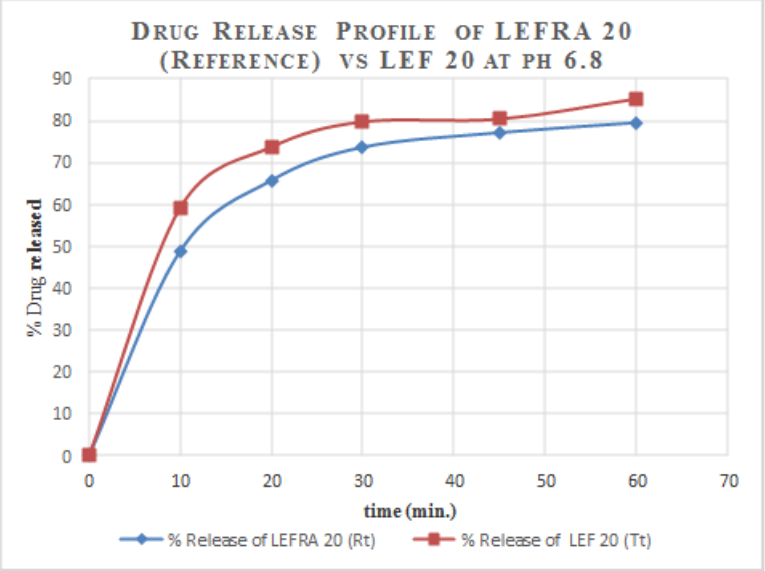

Figure 4: Drug release profile of Reference Product (Lefra-20) vs. Test (Lef-20) at pH 6.8.

Figure 4 demonstrates that the similarity factor of reference vs. test products at pH 6.8 is 55.18 which show they both have acceptable and similar release patterns.

4. CONCLUSION

The similarity factor (f2) between reference product and test product was found to be 62.76, 52.03 and 55.18 in dissolution medium of pH 1.2 HCL, pH 4.5 Buffer and pH 6.8 Buffer respectively which lies within the required range of above 50. Thus, we can conclude that the dissolution profile of test product (Lef- 20) is similar in comparison to that of reference product (Lefra- 20).

5. ACKNOWLEDGEMENT

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development of Test Product (Lef-20).

6. Conflict of Interest

The author declares no conflict of interest and no third party funding in this study.

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