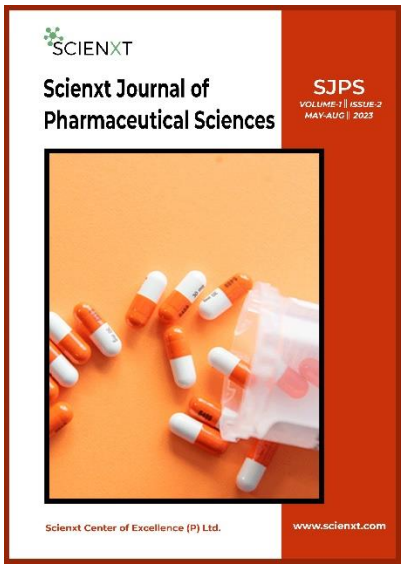

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Comparative analysis of ofloxacin tablets: Assessing bioequivalence and post-compression parameters in brand, generic, and in-house formulations

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Abstract:

Ofloxacin is a second generation Fluoroquinolone, whose primary mechanism of action is the inhibition of bacterial DNA gyrase. It is used widely for the therapy of mild-to-moderate bacterial infections. Various brand and generic versions of Ofloxacin tablets are available in the market with the general claim that they all are bioequivalent. In the present study, an attempt is made to compare and evaluate post compression parameters of brand, generic and prepared Ofloxacin tablets containing 200 mg of the drug and to determine whether all formulations used were equivalent or significantly different. Ofloxacin tablets were prepared by wet granulation method by using different ingredients like carboxy methyl cellulose and dicalcium phosphate. All the formulations including brand, generic and prepared Ofloxacin tablets were analyzed for their weight variation, hardness, friability, drug content, in vitro disintegration and in vitro dissolution profile and results were found to be present within the prescribed limit. The drug release from branded drug products was slightly higher compared to generic drug products procured from the market and prepared in-house. All the findings and outcomes have shown that brand, generic and prepared formulations exhibit better response.

Keywords:

ofloxacin tablets, Fluoroquinolone, Generic drugs, FDA standards, critical manufacturing variables

1. Introduction:

Brand and generic drugs are the two major categories of medicines in the pharmaceutical market. These systems are similar in the amount of drug, color, shape, weight, preparation method and fabrication. In contrast, they may have differences in their formulation and excipients used. Generic drugs cost less than their brand name counterparts due to several reasons research costs branded drugs to prove their safety and efficacy have to go through various animal and clinical studies whereas generic benefit from a reduction in upfront research cost. Lower prices generally go hand in hand with more competition.[1]

Generic drugs should meet FDA standards for market approval like pharmaceutically equal, same amount of active ingredients as that of the branded version, inert inactive ingredients, have suitable packaging and labeling and patents have expired on branded drugs, etc.[2]

To determine the influence of critical manufacturing variables, comparative studies on in vitro in vivo correlation and maintaining quality control procedures in R&D dissolution testing have been widely employed. A dissolution study is considered the most important tool for predicting in vivo bioavailability, and in some cases, it bypasses clinical studies to determine bioequivalence. To evaluate the quality of the product, to confirm product consistency during its life cycle, dissolution tests are commercially used, and to assess post-approval changes and the need for bioequivalence studies.[3]

Immediate-release tablets are formulated in such a way that they break down rapidly within minutes and get dissolved to release the medicaments and achieve a rapid onset of action. The oral route is the most preferred route for drug administration because of its various advantages like systemic effect, ease of administration, self-administration and high levels of patient compliance.[4]

In this study, we compared the in vitro parameters of branded, generic and self-prepared formulations of the drug ofloxacin. Ofloxacin is a type of fluoroquinolone antibiotic that belongs to the second generation of this class of drugs. It is a more potent version of norfloxacin and has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. It was first approved for use in Japan in 1985 under the brand name Tarvid for the treatment of various infections such as respiratory tract infections, skin and skin structure infections, urinary tract infections, prostatitis, and sexually transmitted diseases. Ofloxacin works by inhibiting two bacterial enzymes called DNA gyrase and topoisomerase IV, which are essential for bacterial DNA replication and cell division... [5]

Ofloxacin is widely indicated in the treatment of bacterial infections such as COPD, Community-acquired pneumonia, skin infection, urethritis, cervicitis and epididymitis.

2. Materials and methods:

2.1. Materials:

The standard ofloxacin was obtained as a gift sample from KAPL, Karnataka. Starch powder, carboxymethyl cellulose, dicalcium phosphate, magnesium stearate and talc were purchased from SD Fine Chemicals, Mumbai, India. All the chemicals and reagents used in the study are of analytical grades.

The Oflomac 200, manufactured by Macleods Pharmaceuticals, and the generic counterpart Oflox 200, manufactured by Simpatico, were acquired from a local pharmacy in Shimoga, Karnataka, India.

3. Methodology:

3.1. Preparation of 0.1 N HCl (pH 1.2):

Dissolve 8.3 ml of concentrated hydrochloric acid in 1000 ml of water to produce 0.1 N HCl solution.

3.2. Determination of λ_{max}:

The standard solution of ofloxacin was scanned for absorption maxima against the blank between 200 to 400 nm using a UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The maximum absorbance was found to be 294 nm.

3.3. Calibration curve of Ofloxacin in 0.1 N HCl:

Accurately weighed 50 mg of pure ofloxacin was transferred into a 100 ml volumetric flask, dissolved and adjusted the volume up to 100 ml with 0.1 N HCl to get stock A. From the stock solution A, 10 ml was pipetted out into a 100 ml volumetric flask and diluted with 0.1 N HCl to make up to 100 ml to get stock solution B. From stock B several volumes were pipetted out and transferred to a 10 ml volumetric flask and make up the volume with 0.1 N HCl and absorbance was obtained at 294 nm by UV- visible spectrophotometer (UV-1601, Shimadzu, Japan) using a suitable blank.

3.4. Preparation of Ofloxacin tablets:

Table. 1: formulation table

Ingredients (mg)	Brand Product	Generic Product	F1	F2
Ofloxacin	200	200	200	200
Carboxymethyl cellulose	-	-	15	15
Dicalcium phosphate	-	-	80	80
Starch paste	-	-	5%	10%
Magnesium stearate	-	-	2	2
Talc	-	-	2.5	2.5
Total	-	-	300	300

The immediate release tablets of Ofloxacin were prepared using the wet granulation method with ofloxacin as the drug. All powders were weighed and thoroughly mixed in a clean and dry mortar. The required amount of starch paste is added to form a coherent mass. Pass coherent mass through the sieve (No16) to obtain granules. Dry the wet granules using a hot air oven until they reach the desired moisture content. After drying, screen (sieve no 60) the granules to remove any oversized or undersized particles. Mix lubricants (magnesium stearate) and glidants (talc) to improve the flow properties. The weighed amount of granules were transferred to the die cavity and punched using 9 mm flat punches using a single-station tablet punching machine (Cadmach machines, Ahmedabad).

3.5. Evaluation of the tablets [7]:

3.5.1. Thickness:

The thickness of each tablet was determined by using a Vernier caliper.

3.5.2. Hardness:

The hardness of tablets was tested using a Monsanto hardness tester. Scale was adjusted to zero and the tablets were held between the spindle and anvil and pressure was applied by these jaws until the tablets were broken. The hardness of tablets is measured in terms of Kg/cm^2. To get

satisfactory quality tablets hardness should be between 4 to 8 Kgandcm2. The average of three readings was noted.

3.5.3. Friability:

The friability of the tablets (brand, generics and developed formulations) was tested by Roche friabilator. Ten tablets were pre weighed and placed in the friabilator. The tablets were allowed to fall from a height of 6 inches for 4 min (25 RPM). After subjecting the tablets to a friability test using a friabilator, they were removed, cleaned of any dust and weighed. The percentage of friability was then calculated using the following equation:

$$F= \frac{W\ initial-(W\ final)}{W\ initial} * 100$$

3.5.4. Variation in weight:

Randomly selected tablets were weighed individually and together in a single pan balance. The deviation of the individual weight of the tablet from the average weight was calculated mathematically. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablets differs by more than double the percentage limit.

$$\%\ Deviation = \frac{W\ avg - W\ individual}{(W\ avg)} * 100$$

Where,

W avg – Average weight of tablets

W individual – Individual weight of tablet.

3.5.5. Amount of active ingredient:

The drug content was determined by extracting the drug from the powdered tablet samples. The powder sample was kept for shaking with 100 ml 0.1 N HCl on a rotary shaker for 48 hrs. Filtered using Whatman filter paper and suitably diluted. It was analyzed by UV-Vis Spectrophotometer (1601, Shimadzu, Kyoto, Japan) using a suitable blank at 294 nm.

$$\text{Drug content (\%)} = \frac{\text{Actual drug content}}{\text{Theoritical drug content}} * 100$$

3.5.6. Disintegration time:

One tablet was placed in each of the 6 tubes of the basket in a disintegration testing apparatus (Rupa Industries, New Delhi). The disk was added to each tube and the apparatus using 0.1 N

HCl maintained at 37±0.5˚C as the immersion liquid. The time taken to disintegrate the tablet was visually noted.

3.5.7. Dissolution studies[8]:

The dissolution studies were performed according to the USP apparatus-2 method (paddle type), and the release profile of Ofloxacin from each branded, generic and prepared tablet was performed using 900 ml of 0.1 N HCl at 37±0.5˚C and 50 rpm. A volume of 5 ml was withdrawn at different time intervals from the dissolution medium and replaced immediately with a fresh medium. The samples were filtered and diluted (if needed) to a suitable concentration with the same dissolution medium and assayed by using a UV spectrophotometer (U V 1601, Shimadzu, Japan) at 294 nm. The cumulative percentage of drug release was calculated using the linear regression equation of the calibration curve. The average of 3 readings was noted and the values are noted.

4. Results and discussion:

4.1. Calibration curve of Ofloxacin:

The pure sample of Ofloxacin was calibrated using 0.1 N HCl (pH 1.2). The calibration curve of Ofloxacin was developed in the range of 2-20 µg/ml at 294 nm. During the procedure, the absorbance seems to increase as the concentration increases, which implies that the tested concentration range obeys Beer's Lambert's law. The standard plot equation obtained was y=0.160(x) +0.002 and the regression coefficient (R^2 value) was 0.999.

Table. 2: Calibration curve of Ofloxacinin 0.1 N HCl solution

Sl. No.	Concentration (µg/ml)	Absorbance (λmax 294 nm)
1	0	0
2	1	0.154
3	2	0.329
4	3	0.500
5	4	0.637

6	5	0.809
7	6	0.961

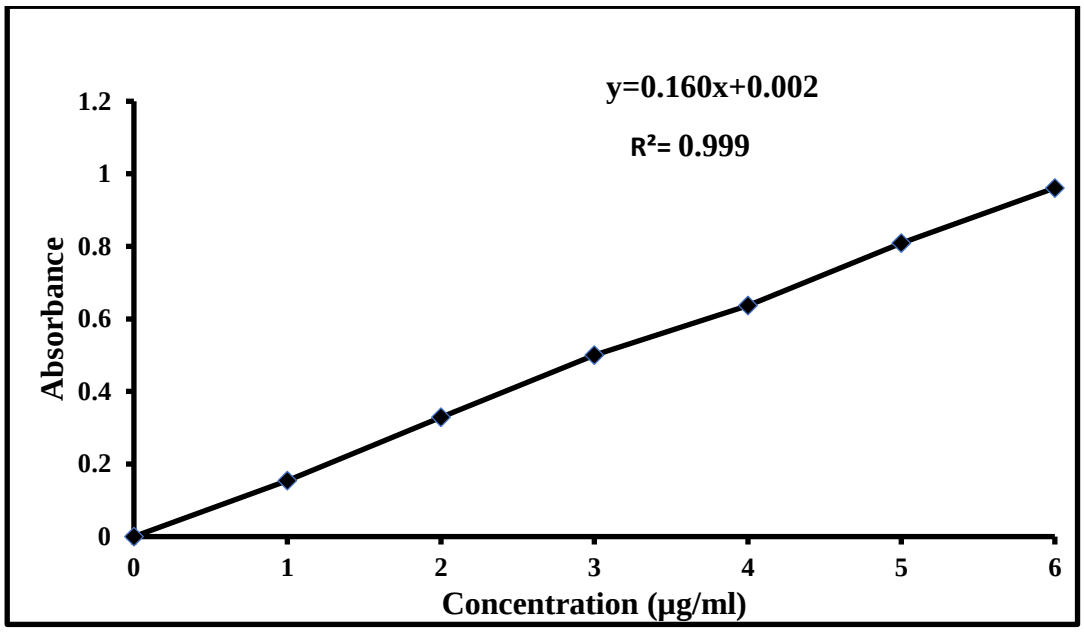

Figure. 1: Calibration curve of Ofloxacin in 0.1 N HCl solution (pH 1.2)

4.2. Evaluation of the formulations:

Table. 3: Evaluation of tablets

Formulation	Hardness ($kg/cm^{2)}$	Friability (%)	Average weight (mg)	Drug content (mg)
Brand	5±0.21	0.97	272±0.05	195.1±0.09
Generics	4.8±0.27	0.41	324±0.037	205.60±0.12
F1	6.8±0.31	0.8	22±0.001	183.12±0.89
F2	6.4±0.34	0.6	299±0.004	175.55±0.76

Values are mean± SD (n=3)

Using a Monsanto hardness tester, the strength of the tablets was tested and the hardness of all tablets was found to be within the acceptable limit (5-8 kg/cm^2). The hardness of the brand and generic formulations was 5 and 4.8 kg/cm^2 respectively. The hardness of the prepared tablets

was also determined and found to be within the range of 6.8 kg/cm² to 6.4 kg/cm² in which F1 showed the lowest hardness value compared with F2, which possessed the highest hardness value.

The percentage friability of brand and generic formulations was found 0.97% and 0.41%, respectively and the % friability of the prepared formulations was within the range of 0.8% to 0.6%, in which the F1 and F2 showed low friability, the friability was within the acceptable limit (less than 1%) and the tablets were mechanically stable.

The weight variation of brand and generic formulations was found in the range of -3.225 % to 2.205 % and 3.86% to 2.77 %, respectively and the weight variation of prepared formulations (F1 & F2) was in the range of -2.161 % to 3.082 % and -0.334 % to 0.334 %, respectively, in which formulation F2 showed the lowest and formulation F1 showed the highest weight variations comparatively. The percentage deviation was within the pharmacopeia limit of ± 5%.

The amount of drug in the brand and generic formulations was found to be 195 mg and 205.6 mg, respectively. For the prepared formulations, the amount of the pure drug present in the formulations was found to be in the range of 183.125 mg to 175.55 mg, and the results for each tablet formulation are given in Table. 3. This was within the acceptable limits mentioned in the official standards.

4.3. In vitro Disintegration Test:

Table. 4: Disintegration time of tablets

Formulation	Disintegration time (min)
Brand	9.35±0.32
Generic	5.18±0.36
F1	13.20±0.87
F2	13.50±0.23

Values are mean± SD (n=3)

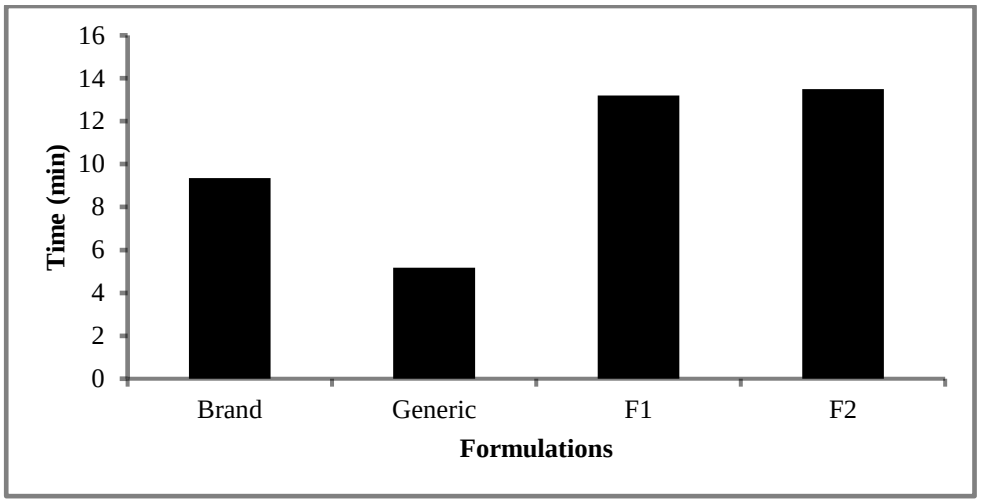

Figure. 2: Comparative graph on disintegration time of different tablets

The observed disintegration time for all ofloxacin formulations was 15 min, which is within acceptable limits. The disintegration times for the brand and generic were 9 min 35 s and 5 min 18 s, respectively. Among the prepared formulations, F1 showed the fastest disintegration time and F2 took more time to disintegrate. Among the formulations, the fastest disintegrated tablet was the generic formulation, whereas the F2 formulation was the slowest.

4.4. In vitro dissolution studies:

Table. 5: In vitro drug release study of brand product in 0.1N HCl

Time (min)	**Cumulative % Drug released**			
	Brand Product	**Generic Product**	**F1**	**F2**
0	0	0	0	0
10	56.82±0.25	53.94±0.26	52.52±0.11	49.35±0.22
20	68.68±0.34	69.24±0.14	60.80±0.19	53.62±0.39
30	77.71±0.27	78.27±0.34	67.59±0.29	57.18±0.29
40	76.79±0.17	87.65±0.17	73.80±0.17	61.85±0.27
50	91.02±0.01	93.03±14	79.11±0.35	66.54±0.31
60	95.26±0.24	94.94±0.26	84.15±0.26	69.44±0.25

Values are mean ± SD (n=3)

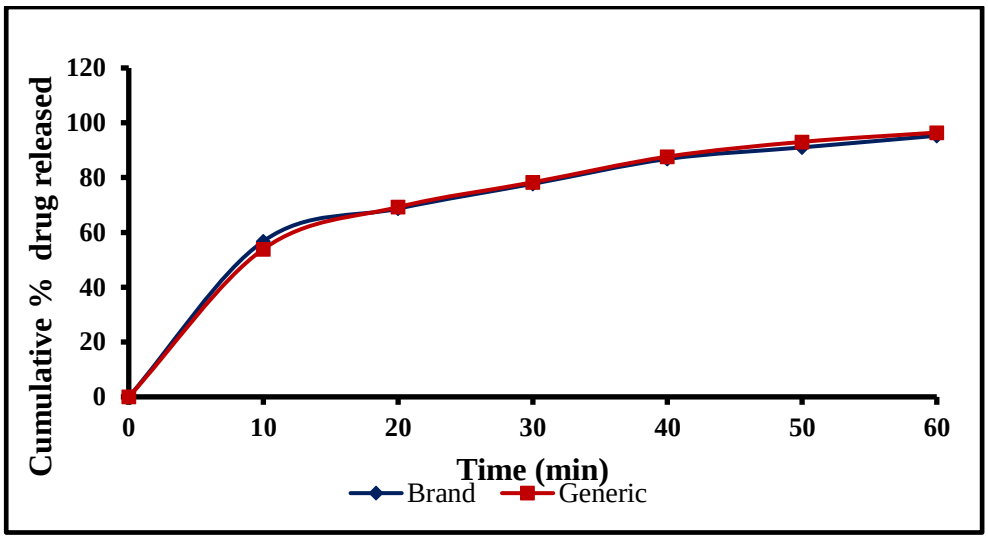

Figure. 3: Comparative plots on in vitro drug release profile of brand and generic product in 0.1N HCl

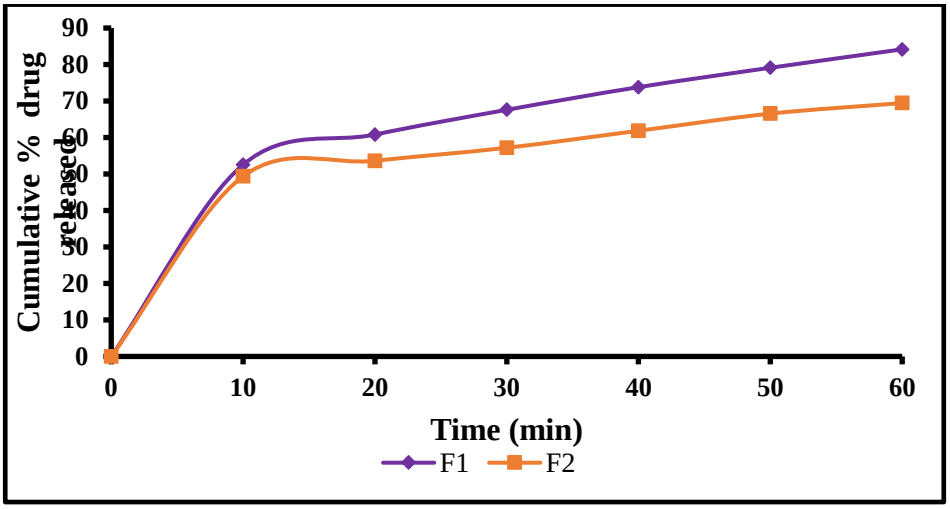

Figure. 4: Comparative plots on in vitro drug release profile of self-prepared formulations in 0.1N HCl

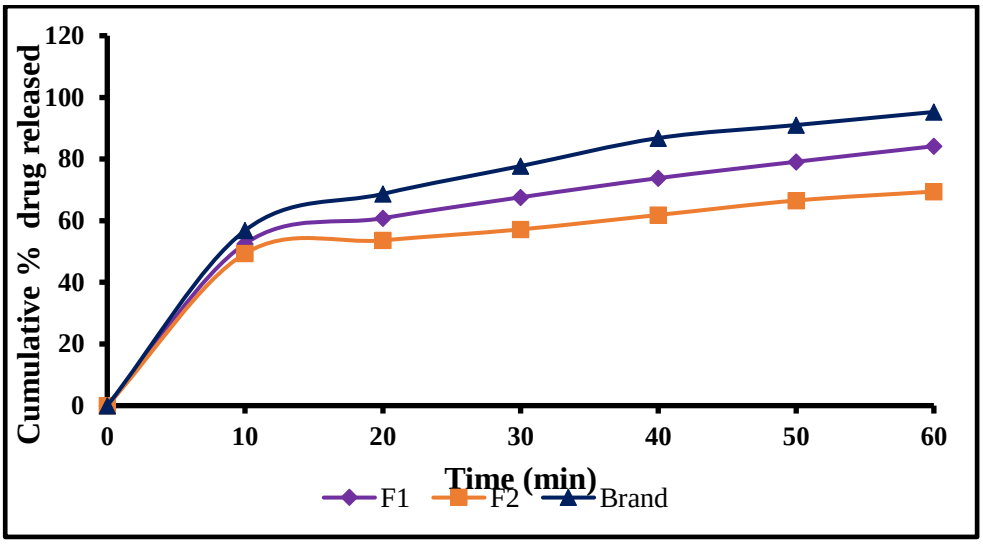

Figure. 5: Comparative plots on in vitro drug release profile of brand and self-prepared formulations in 0.1N HCl

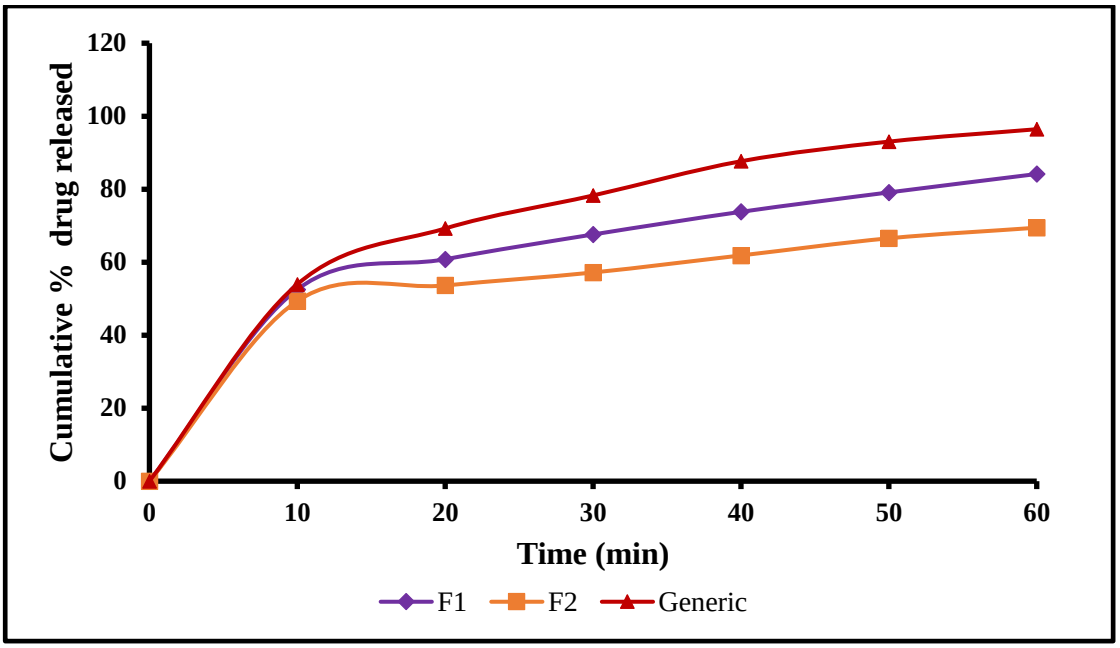

Figure. 6: Comparative graph on in vitro drug release profile of generic and self-prepared formulations in 0.1N HCl

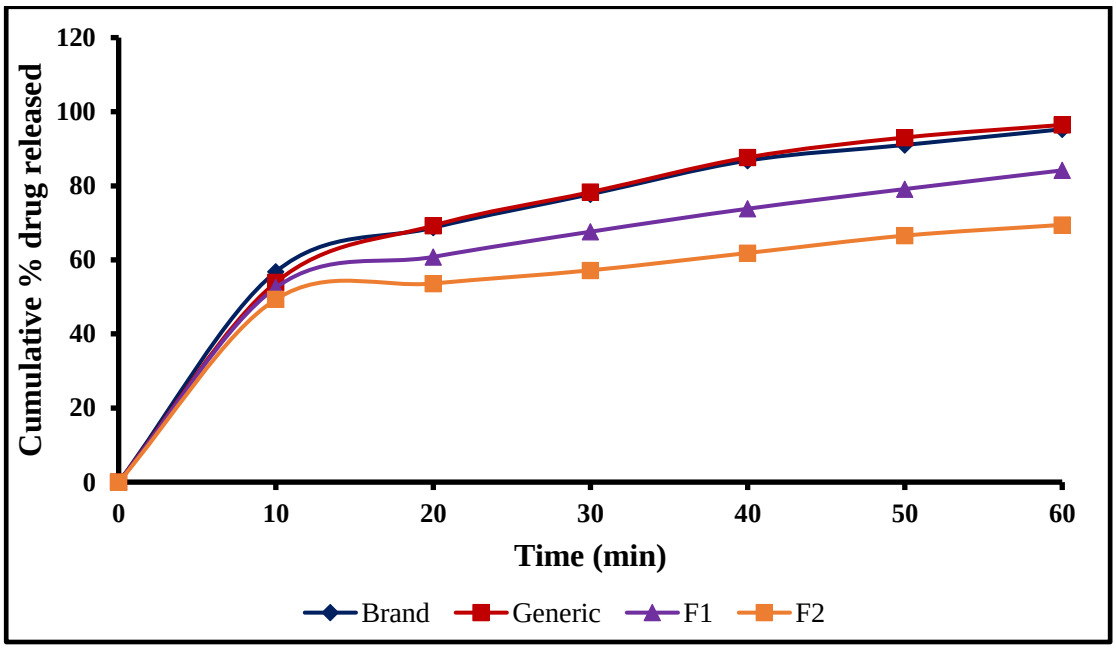

Figure. 7: Comparative plots on in vitro drug release profile of brand, generic and self-prepared formulations in 0.1N HCl

The drug release studies were conducted in 0.1 N HCl (pH-1.2) for 60 min. In-vitro release data for all formulations are provided in Table 5 and the release profiles are shown in Figures 3-7. In the in-vitro drug release study conducted for the brand and generic products, the cumulative percent drug release obtained was 95.26% and 96.42% respectively at 60 min. In the case of prepared formulations F1 and F2, the cumulative percent drug release was found to

be 84.15% and 69.44 % respectively. When the cumulative percent drug release of the brand and generic were compared with each other, the cumulative percent drug release of the brand was almost similar to the generic product.

Amongst the prepared formulations, formulation F1 showed higher drug release compared to formulation F2. The formulations branded, generic, F1 and F2 possessed all the desired properties of immediate release formulations.

5. Conclusion:

In this study, we conducted a comparison of the innovator drug product (oflomac 200) and generic drug product (oflox 200) and prepared formulations based on various physical parameters. Overall, the physical characteristics of the formulations were largely similar, with the notable exception being the dissolution of the drug. The brand products exhibited nearly similar drug release profiles to the generic product and demonstrated comparatively higher drug release than the prepared formulations. However, it is worth noting that by making minor adjustments to the formulation and preparation methodology, it may be possible to develop a generic product with a drug release profile similar to that of the branded product, potentially achieving bioequivalence.

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