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Comparative In-Vitro Bioequivalence Evaluation of Different Brands of Indomethacin Capsule

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ABSTRACT

Indomethacin is a drug belongs to class NSAIDs used in the treatment of inflammatory rheumatoid diseases and relieve acute pain, period pain and pain after surgery and fever. This study aimed at evaluating some quality control parameters to compare the quality, safety, and efficacy of three brands of Indomethacin capsules available in the Indian market. In the present study three marketed formulations of Indomethacin of 25 mg strength were analyzed with quality parameters like Weight variation test, Disintegration test and In-vitro bioequivalence study with developed spectrophotometric analytical method. The Indomethacin capsule, Microcid exhibited highest in-vitro drug release 97.05% and lowest Disintegration time 320 sec. compared to other brands of Indomethacin capsule.

Keywords: Indomethacin, In-vitro release study, Spectrophotometric analysis method development, Bioequivalence.

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INTRODUCTION

Indomethacin is practically insoluble in water. It is soluble in ethanol, ether, acetone & castor oil. Indomethacin as a free base is soluble in 1gm/50ml ethanol, 1gm/30ml chloroform & 1gm/40-45ml diethyl ether. However, it should be noted that it is not stable in alkaline solution. Indomethacin solution below pH 7.4 was stable[1].

Capsules are solid dosage form in which one or more medicaments are enclosed in water- soluble, biodegradable shell made up of gelatin. Capsules are gelatin shells filled with the ingredients that make up an individual dose. Dry powders, semi-solids, and liquids that do not dissolve gelatin may be encapsulated. Capsules account for about 20% of all prescriptions dispensed[2,4].

After granting of product from marketing authorization, post market survey or monitoring is very important and it involves all activities to obtain more data and information about a product. Regulatory agencies uses only limited information obtained during clinical trials and to some extent scientific literature as guides to grant marketing authorization of medicines for public use, and hence it is essential to conduct post market survey or monitoring of marketed products to assess the therapeutic effectiveness, quality and safety of medicines for the larger public3,4. The aim of this study was to compare the physicochemical parameters and assay of the three brands of Indomethacin tablets.

MATERIALS AND METHOD

Indomethacin was procured from Micro Labs Ltd., Indocap® 25mg, Microcid ® 25mg, Donica ® 25mg was purchased from Jagsonpal Pharmaceuticals and Ipca laboratories Ltd.

Selection of solvent:

The Methanol was selected as dissolution media because it represents the P^H of gastrointestinal fluid.

Solubility of Indomethacin in Methanol[7]:

Solubility of drug in Methanol was determined by dissolving the known quantity drug in cumulative manner with the aid of sonication till the drug remains soluble[5,6].

Determination of λ_{max}[8]:

The absorption of Indomethacin was determined by running the spectrum of the drug solution in UV Spectrophotometer Agilent Carry 60.

Procedure:

Accurately weighed 10 mg of drug was dissolved in 100 ml of Methanol in 100ml volumetric flask with aid of sonication in bath sonicator for 20 minutes. This solution was labeled as stock-1. From

the stock -1, 1 ml of the solution was withdrawn and diluted with water in 10 ml volumetric flask (10µg/ml). This solution was labeled as stock-2. From the stock-2, 5 ml of the solution was withdrawn and diluted up to 10ml with water in 10 ml volumetric flask (50µg/ml) and analyzed against the corresponding reagent blank, the characteristics peak of Indomethacin was found at 340nm in UV spectrophotometer (Agilent Carry 60).

The Indomethacin showed the absorbance maxima at 340 nm in methanol.

LINEARITY AND RANGE[9]:

Linearity:

The linearity of an analytical procedure is its ability (within a given range) to obtain test result which are directly proportional to the concentration (amount) of analyte in the sample.

A linear relationship should be evaluated across the range of the analytical procedure. It may be demonstrated directly on the active substance (by dilution of a standard stock solution) and/or on separate weighing of systemic mixtures of the product component, using the proposed procedure a latter aspect can be studied during investigation of the range.

Range:

The range of an analytical procedure is the interval between the upper and lower concentration (amount) of analyte in the sample (including this concentration) or which it has been demonstrated that the analytical procedure has a suitable level of a precision, accuracy and linearity.

Procedure:

The main stock solution was prepared by dissolving accurately weighed 10 mg of drug dissolved in 100 ml of methanol in 100 ml volumetric flask. With the aid of sonication, it was diluted up to 10 ml in 10 ml volumetric flask, this solution was labeled as stock- 2. From the stock 1, 2, 3, 4, 5 ml solutions were withdrawn and diluted up to 10ml with water in 10 ml volumetric flask to get concentrations of 10 to 50 µg/ml respectively.

The absorbance of each solution was measured at 340 nm using methanol. This experiment was performed in replicate of three and the average of absorbance was calculated and curve of absorbance versus concentration was plotted.

Weight variation test[3,10]:

10 capsules were taken at random and weighed. Their average weight was calculated, then each capsule was weighed individually and their weights were noted. The contents from the shells were removed just by emptying or with the help of small brush.

Dissolution test:

Preparation of standard plot:

100 mg of pure drug (Indomethacin) was dissolved in 10 ml of methanol and diluted up to 100 ml with phosphate buffer in volumetric flask. From this stock solution 10 ml was withdrawn in another volumetric flask and diluted up to 100 ml with phosphate. Different concentrations were prepared from above second stock solution like 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml. Absorbance above working solutions were measured by UV spectrophotometer (Agilent Carry 60)[3,10].

Procedure:

Dissolution apparatus (Veego, 8 Jar) was used for dissolution study; 750 ml of Phosphate buffer (PH 7.2) was used as a dissolution medium, and operated at 100 rpm for 20 min. A suitable volume of the sample was withdrawn after every 5 min. and each sample was filtered promptly through a membrane filter disc which has an average pore diameter not greater than 1.0 µm. The first few ml of filtrate was rejected each time and a suitable volume of each filtrate was diluted with the same solvent. Absorbance was measured by using UV spectrophotometer (Agilent Carry 60) of the resulting solution at the maximum at 340 nm[11].

Disintegration test:

One dosage unit in each of the six tubes of the basket was placed and a disc was inserted inside the basket. The apparatus was operated using water as the immersion fluid unless another liquid is specified and temperature was maintained at 35-39 °C. At the end of the specified time, the basket was lifted from the fluid and the dosage units observed, all of the dosage units have disintegrated completely. The requirements of the test are met if not less than 16 of the 18 dosage units tested are disintegrated[10].

RESULTS AND DISCUSSION

Linearity and Range:

A linear relationship across the range of concentrations and suitable level of a precision & accuracy was observed as shown in Figure 1 & Table 1.

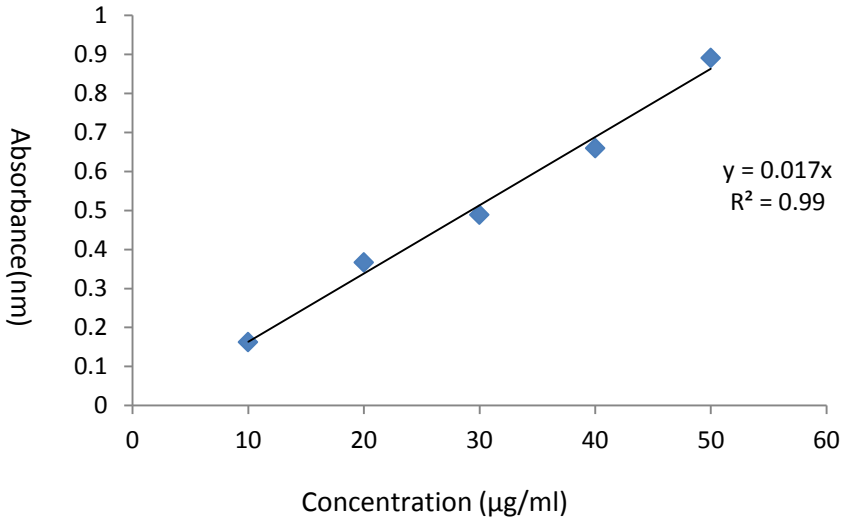

Figure 1: Standard curve of Indomethacin at 340 nm

Weight variation test:

The percent weight variation of all formulations is within standard limits as shown in Table 2.

Table 1. Calibration curve of Indomethacin

Sr. No.	Concentration (µg/ml)	Absorbance*
1	10	0.1623
2	20	0.3666
3	30	0.4887
4	40	0.6594
5	50	0.8906

*Average of three determinations

Table 2. Weight variation test of all marketed formulations:

Sr. No.	Formulations	Weight of Capsule (gm)	Wt. of Empty Shell (gm)	Wt. of Content (gm)	% Weight variation
1.	Indocap (25mg)	0.3756	0.0611	0.3108	Within limit
2.	Microcid (25mg)	0.2574	0.0505	0.2079	Within limit
3.	Donica (25mg)	0.2036	0.0414	0.1609	Within limit

Disintegration time:

Disintegration time of all marketed formulations were studied and observed that, Microcid® has short disintegration time of 320 Sec than other formulations as shown in Table 3.

Table 3. Disintegration test of all marketed formulations:

Sr. No.	Formulations	Average Disintegration Time(sec.) of 6 Capsules
1.	Indocap®25mg	332
2.	Microcid®25mg	320

3.	Donica®25mg	325

Dissolution test:

Dissolution profile of each marketed formulation were studied and observed that dissolution rate of Microcid® was 97.05% which shows better release profile than other formulations as shown in Figure 2 and Table 4.

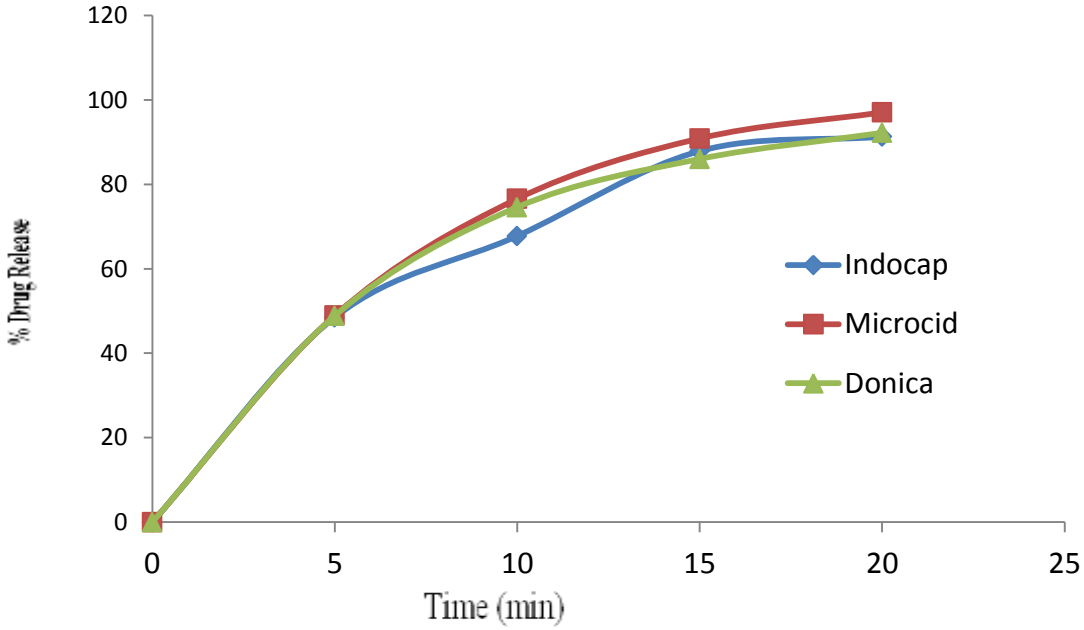

Figure 2: Time Vs Comparative % Drug release of all marketed formulations

Table 4. Comparative % drug release of all marketed formulations:

Time (min)	% drug release		
	Indocap	**Microcid**	**Donica**
5	48.52	48.93	48.87
10	67.77	76.58	74.60
15	87.88	90.88	86.02
20	91.28	97.05	92.20

CONCLUSION

Comparative bioequivalence study of Indomethacin of various marketed formulations was carried out by estimating different parameter like Spectrophotometric analysis, Weight variation, Disintegration test, In-vitro drug release studies. From the result of these parameters it was concluded that Microcid® of Micro labs Ltd (25mg) is a better formulation than other formulations of Indomethacin as it shows better release profile and Disintegration time. UV Spectrophotometric analytical method was developed and found linear, accurate, precise and was also easy to carry

out. The data and information so obtained could be employed for product improvement, development of standards and regulations.

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