

## Bioavailability Study of Sustain Release Preparations of Three Widely used NSAIDS Available in Bangladesh

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Received date: Apr 24, 2016; Accepted date: May 20, 2016; Published date: May 23, 2016

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### Abstract

This research has been designed to assess the in vitro bioavailability study of widely distributed and commonly used three analgesic and anti-pyretic drugs namely Diclofenac Sodium, Paracetamol and Ibuprofen sustained release tablets. Three brands of Diclofenac Sodium, four brands of Paracetamol and three brands of Ibuprofen tablets were obtained. Three brands of Diclofenac SR tablets, all brands maintained a steady state release pattern throughout the defined period, i.e. 12 hours. In 1st hour sample D01, D02, D03 were released 43.6%, 36.16%, and 59.85% of drug in dissolution respectively. Four brands of Paracetamol SR tablets, all brands maintained a steady state release pattern throughout the defined period, i.e. 12 hours. In 1st hour sample P01, P02, P03 and P04 were released 78.60%, 89.36%, 74.21%, 78.14 of drug in phosphate buffer (pH 6.8) respectively. Another sustained release tablets was Ibuprofen; all brands maintained a steady state release pattern trough out the defined period, i.e. 12 hours. In 1st hour sample I01, I02, I03 were released 60.46%, 54.02%, 50.57% of drug in phosphate buffer (pH 6.8) respectively. The release rates of the samples were determined for around 12th hours.

### Key Words:

Bioavailability; Dissolution; Release Kinetics; Bangladesh

### Introduction

In Vitro dissolution is one of the most important tools to forecast the in-vivo bioavailability and in some cases to determine bioequivalence and assure interchangeability [1]. It is a cheap and suitable testing way to predict absorption and bioavailability differences among tablets and capsules formulation [2].

Formulation and manufacturing properties is important for the efficacy of pharmaceutical dosage forms. In vitro dissolution tests can be help to pharmaceutical formulation developments identifying critical manufacturing parameters which are require to both bioavailability and bioequivalence.

Paracetamol is a familiar OTC (Over- the-counter) analgesic and antipyretic drug. Paracetamol is sparingly water soluble and prone to dissolution and bioavailability problems [3-5]. It is prescribed most frequently for the treatment of fever, headache, and other aches. Chemically paracetamol is known as acetaminophen. Paracetamol can cause fatal liver damage in case of overdose [6-8].

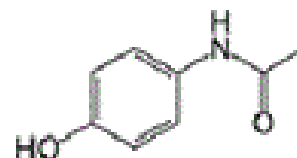


Figure 1: Structure of Paracetamol

Diclofenac Sodium, one of the most useful NSAIDs agent, it is a practically insoluble compound in acidic solution (pKa=4.0), but dissolves in intestinal fluid and water [9]. Diclofenac Sodium is official in the Martindale Extra Pharmacopoeia. Therefore this drug is an ideal candidate for develop in lease dosage form which could result in prolonged clinical efficacy reduced frequency of administration and less side effects [10].

Diclofenac sodium extended-release tablets that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models and it is used for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [11-13]. As with other NSAIDs, diclofenac is known to increase the risk of cardiovascular side effects and GI bleeding. However, diclofenac has a relatively high therapeutic index in comparison to other NSAIDs [14-16]. Due to its clinical effect and short biological half-life ,diclofenac-based pharmaceuticals are ideal candidates for prolonged release formulations [17].

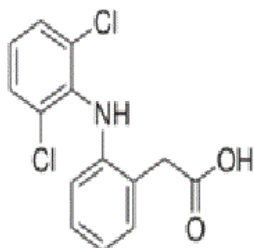


Figure 2: Structure of Diclofenac Sodium

The model drug is ibuprofen, widely used NSAIDs. It is an analgesic, anti-inflammatory and anti-pyretic agent [18]. It is used to reduce the tenderness, pain, inflammation and stiffness caused by gout and arthritis. Diclofenac Sodium is also used to relief fever, headache, muscle aches, menstrual pain, aches and pain from the common cold, backache and pain after surgery or dental work. Ibuprofen is a major medicine in the World Health Organization's "Essential Drugs List", that means it is in list of minimum medical needs for basic health care system [19]. It is soluble in water and aqueous fluids. Solubility enhancers are requiring for increasing the dissolution rate which is require to better bioavailability [20].

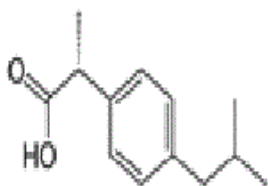


Figure 3: Structure of Ibuprofen

## Materials and Methods

Reference standard of Diclofenac Sodium, Paracetamol and Ibuprofen were collected from Techno Drugs Limited. All reagents were analytical grade using for in vitro bioavailability study such as hydrochloric acid (Merck, Germany); Potassium Chloride (Merck, Germany).

## Instruments

A double beam Shimadzu UV-visible spectrometer (UV mini-1700, Shimadzu Corporation, Kyoto, Japan with 1 cm quartz cells). HANNA HI 2211 pH meters (Romania). An Automated Eight Basket Tablet Dissolution Tester UDA-80 USP Standard (Veego, India) was used.

## Collection of Samples

Ten brands of Paracetamol, Ibuprofen and Diclofenac Sodium (check manufacturing date not exceed more than four months) were purchased from various drug shops of Dhaka city in Bangladesh. The samples were properly checked for their manufacturing batch number or product batch number, license number, manufacturing date and

expiring dates before collection. For Diclofenac Sodium, Paracetamol and Ibuprofen they were randomly coded such as DO1, DO2, DO3, P01, P02, P03, P04 and I01, I02, I03. The collected samples were stored  $25 \pm 2^\circ\text{C}$  for four weeks before the dissolution study for the consequence of organoleptic changes.

## Preparation of standard curve of Paracetamol

100 mg Paracetamol powder (99.5% pure) was taken in a 100 ml volumetric flask and added with 10 ml 0.1N NaOH solution. Then gently shaken the flask for 15 minutes to dissolve the powder. Solution was made upto 100ml by adding phosphate buffer.

From this stock solution 1ml, 2ml, 3ml, 4ml, and 5ml solutions were taken into 100 ml volumetric flask and made them up to the mark with phosphate buffer to obtain 0.01mg/ml, 0.02 mg/ml, 0.03 mg/ml, 0.04 mg/ml and 0.05mg/ml concentration of the solution respectively. Absorbances of the all solutions were measured at 257nm by using UV Spectrophotometer. The observation were recorded and graphically presented to obtain standard curve of paracetamol.

## Preparation of standard curve of Diclofenac Sodium

Stock solution was prepared by dissolving 100 mg of Diclofenac Sodium powder (100.5% pure) in 100 ml phosphate buffer. From this stock solution 1ml, 2ml, 3ml, 4ml, and 5ml solution were taken into 100 ml volumetric flask and made them up to the mark with phosphate buffer to obtain 0.01mg/ml, 0.02 mg/ml, 0.03 mg/ml, 0.04 mg/ml and 0.05mg/ml concentrated solution respectively. Absorbances of the all solutions were measured at 277nm by using UV Spectrophotometer. The observation were recorded and graphically presented to obtain standard curve of Diclofenac Sodium.

## Preparation of standard curve of Ibuprofen

100 mg Ibuprofen powder (99.5% pure) was taken in a 100 ml volumetric flask and added with 10 ml of phosphate buffer (pH 6.8). Then gently shaken the flask to dissolve the powder. Solution was made 100 ml by adding phosphate buffer.

From this stock solution 1ml, 2ml, 3ml, 4ml, and 5ml solution were taken into 100 ml volumetric flask and made up to the mark with phosphate buffer to obtain 0.01mg/ml, 0.02 mg/ml, 0.03 mg/ml, 0.04 mg/ml and 0.05mg/ml concentrated solution respectively. Absorbances of the all solutions were measured at 221nm by using UV Spectrophotometer. The observation were recorded and graphically presented to obtain standard curve of Ibuprofen.

## In vitro dissolution study of collected sustained release dosage form samples

At first 900 ml of the dissolution medium (phosphate buffer pH 6.8) was taken each vessel of the dissolution apparatus. Placed one tablet in a vessel. Immediately placed the tablet in the vessel and started rotating the paddles at the 50 rpm.

During the process maintain a temperature of dissolution medium at  $37 \pm 0.5^\circ\text{C}$ . Every after 1hour time interval withdrawn 5 ml of specimen from the midway of the vessel. Replaced the aliquots withdrawn for analysis with equal volumes (5 ml) of fresh dissolution medium. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times. Continue the test up to the claimed time duration (e. g 12th hours). Measured

the absorbance of the collected sample by using UV Spectrophotometer at 257nm, 277nm and 221nm for paracetamol, diclofenac sodium and ibuprofen preparations respectively and calculate % of release from the data. Repeat the test thrice for better result [21-25].

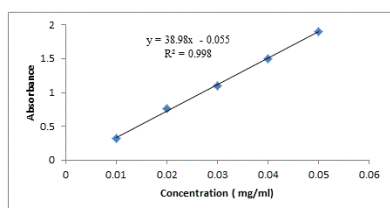
**Preparation of 0.1N NaOH solution:** To prepare 100ml 0.1N NaOH solution, 4gm dehydrated NaOH were accurately weighted and taken in a volumetric flask. Added some distilled water, shaken gently to dissolve the powder. After dissolving the powder added water up to the mark to make it 100ml [26].

**Preparation of Phosphate Buffer (pH 6.8):** Dissolve 28.80 g of disodium hydrogen orthophosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) and 11.45 g of potassium dihydrogen orthophosphate ( $\text{KH}_2\text{PO}_4$ ) in sufficient water to produce 1000 ml and adjust the (pH to  $6.8 \pm 0.05$ ) [27].

## Results and Discussions

### Calibration curve of Paracetamol in phosphate buffer (pH 6.8)

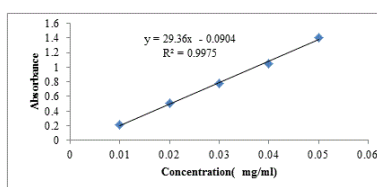
The solution of paracetamol in the concentration of 0.01 to 0.05mg/ml were prepared in phosphate buffer (pH 6.8) and obtained the absorbance using UV spectroscopy. The absorbencies were presented in the figure 4.



**Figure 4:** Calibration curve of of Paracetamol in Phosphate Buffer (pH 6.8)

### Calibration curve of Diclofenac Sodium in phosphate buffer (pH 6.8)

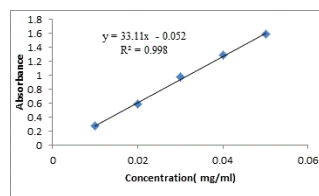
The solution of diclofenac sodium in the concentration of 0.01 to 0.05mg/ml were prepared in phosphate buffer (pH 6.8) and obtained the absorbance using UV spectroscopy. The observations were presented in the following figure 5.



**Figure 5:** Calibration curve of Diclofenac Sodium in Phosphate Buffer (pH 6.8)

### Calibration curve of Ibuprofen in phosphate buffer (pH 6.8)

The solution of ibuprofen in the concentration of 0.01 to 0.05mg/ml were prepared in phosphate buffer (pH 6.8) and obtained the absorbance using UV spectroscopy. The observations were presented in the following figure 6.



**Figure 6:** Calibration curve of Ibuprofen in Phosphate Buffer (pH 6.8)

Time Interval	% Release $\pm$ SD									
	D01	D02	D03	P01	P02	P03	P04	I01	I02	I03
0 hr	0	0	0	0	0	0	0	0	0	0
1st hr	43.60 $\pm$ 1.06	36.16 $\pm$ 0.28	59.85 $\pm$ 1.02	78.60 $\pm$ 0.46	89.36 $\pm$ 0.03	74.21 $\pm$ 0.26	78.14 $\pm$ 0.47	60.46 $\pm$ 1.04	54.02 $\pm$ 0.40	50.57 $\pm$ 1.03
2nd hr	45.82 $\pm$ 0.78	46.40 $\pm$ 0.80	60.85 $\pm$ 0.94	79.16 $\pm$ 0.38	91.24 $\pm$ 0.44	82.24 $\pm$ 1.11	83.53 $\pm$ 0.73	64.13 $\pm$ 0.78	56.72 $\pm$ 0.16	52.55 $\pm$ 0.38
3rd hr	47.30 $\pm$ 0.29	47.08 $\pm$ 0.76	64.84 $\pm$ 0.41	79.72 $\pm$ 0.27	91.37 $\pm$ 0.93	87.64 $\pm$ 0.56	84.96 $\pm$ 0.22	66.87 $\pm$ 0.29	61.23 $\pm$ 0.45	59.49 $\pm$ 1.12
4th hr	47.30 $\pm$ 1.12	47.76 $\pm$ 0.61	67.83 $\pm$ 0.99	81.11 $\pm$ 1.06	92.31 $\pm$ 0.27	89.72 $\pm$ 0.78	86.17 $\pm$ 1.40	71.46 $\pm$ 1.12	63.93 $\pm$ 0.47	67.42 $\pm$ 1.17
5th hr	48.78 $\pm$ 0.59	49.12 $\pm$ 1.19	71.82 $\pm$ 0.27	84.45 $\pm$ 0.51	94.90 $\pm$ 0.63	90.55 $\pm$ 0.17	89.24 $\pm$ 0.18	73.29 $\pm$ 0.59	64.83 $\pm$ 0.87	74.36 $\pm$ 0.87
6th hr	49.52 $\pm$ 1.11	49.12 $\pm$ 0.77	74.81 $\pm$ 0.78	84.45 $\pm$ 0.99	95.80 $\pm$ 0.12	92.47 $\pm$ 0.37	94.33 $\pm$ 0.30	76.95 $\pm$ 0.11	65.53 $\pm$ 0.28	75.35 $\pm$ 1.02

7th hr	51.00 ± 0.87	49.81 ± 0.98	75.81 ± 0.94	87.23 ± 0.85	96.07 ± 1.02	94.30 ± 0.64	95.53 ± 0.93	77.87 ± 0.87	68.43 ± 0.80	77.33 ± 0.72
8th hr	51.73 ± 1.07	49.81 ± 1.03	76.81 ± 1.12	95.16 ± 1.12	96.20 ± 0.49	95.41 ± 0.53	96.87 ± 0.29	86.11 ± 0.76	76.53 ± 0.76	82.29 ± 0.23
9th hr	53.95 ± 0.73	50.49 ± 0.18	80.8 ± 0.44	96.98 ± 0.98	97.12 ± 0.98	97.89 ± 0.77	98.11 ± 0.78	88.87 ± 0.27	77.43 ± 0.61	87.25 ± 0.57
10th hr	57.65 ± 0.40	63.45 ± 0.12	85.79 ± 0.79	97.99 ± 0.37	98.11 ± 0.34	98.10 ± 0.65	98.77 ± 0.67	88.87 ± 1.07	82.84 ± 1.19	89.24 ± 0.45
11th hr	91.64 ± 0.16	81.2 ± 0.20	92.77 ± 0.31	98.99 ± 1.05	98.09 ± 0.76	98.24 ± 0.89	99.00 ± 1.08	94.36 ± 0.98	89.14 ± 0.77	96.18 ± 0.99
12th hr	96.40 ± 0.45	97.57 ± 0.94	95.15 ± 0.38	99.00 ± 0.33	98.87 ± 0.79	98.48 ± 0.67	99.00 ± 0.88	96.19 ± 0.73	92.74 ± 0.98	97.15 ± 0.21

**Table 1:** In vitro dissolution of sustained release Diclofenac Sodium, Paracetamol and Ibuprofen Tablets

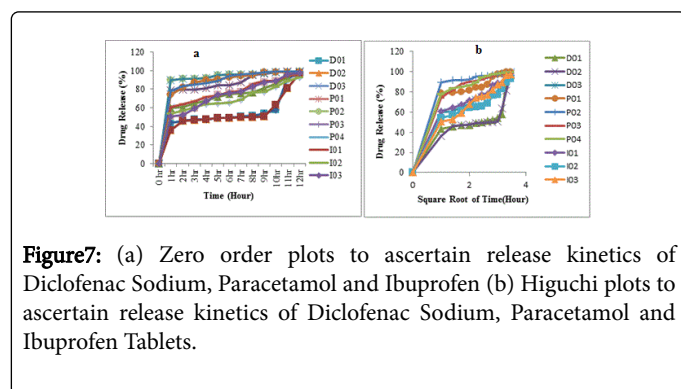
Time Interval	Percentage (%) remaining of sustained release Diclofenac Sodium, Paracetamol and Ibuprofen Tablets									
	D01	D02	D03	P01	P02	P03	P04	I01	I02	I03
0 hr	100	100	100	100	100	100	100	100	100	100
1st hr	56.4	63.84	40.15	21.4	10.64	25.79	21.86	39.54	45.98	49.43
2nd hr	54.18	53.6	39.15	20.84	8.76	17.76	16.47	35.87	43.28	47.45
3rd hr	52.7	52.92	35.16	20.28	8.63	12.36	15.04	33.13	38.77	40.51
4th hr	52.7	52.24	32.17	18.89	7.69	10.28	13.83	28.54	36.07	32.58
5th hr	51.22	50.88	28.18	15.55	5.10	9.45	10.76	26.71	35.17	25.64
6th hr	50.48	50.88	25.19	15.55	4.20	7.53	5.67	23.05	34.77	24.65
7th hr	49.00	50.19	24.19	12.77	3.93	5.7	4.47	22.13	31.57	22.67
8th hr	48.27	50.19	23.19	4.84	3.80	4.53	3.13	13.89	23.47	17.71
9th hr	46.05	49.51	19.2	3.02	2.88	2.11	1.89	11.13	22.57	12.75
10th hr	42.35	36.55	14.21	2.01	1.89	1.90	1.23	11.13	17.16	10.76
11th hr	8.36	18.8	7.23	1.01	1.91	1.76	1.00	5.64	10.86	3.82
12th hr	3.6	2.43	4.85	1.00	1.13	1.52	1.00	3.81	7.26	2.85

**Table 2:** Percentage (%) remaining of sustained release Diclofenac Sodium, Paracetamol and Ibuprofen Tablets

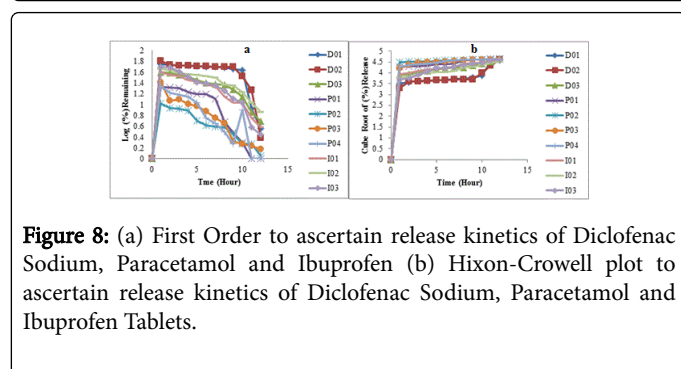
Time Interval	Percent (%) log of remaining of sustained releases Diclofenac Sodium, Paracetamol and Ibuprofen Tablets									
	D01	D02	D03	P01	P02	P03	P04	I01	I02	I03
0 hr	0	0	0	0	0	0	0	0	0	0
1st hr	1.75	1.81	1.60	1.33	1.02	1.41	1.34	1.60	1.66	1.69
2nd hr	1.73	1.73	1.59	1.32	0.94	1.07	1.22	1.55	1.64	1.68
3rd hr	1.72	1.72	1.55	1.31	0.925	1.09	1.18	1.52	1.59	1.61
4th hr	1.72	1.72	1.51	1.23	0.885	1.01	1.14	1.45	1.56	1.51
5th hr	1.71	1.71	1.45	1.19	0.71	0.97	1.03	1.43	1.55	1.41
6th hr	1.70	1.71	1.40	1.19	0.62	0.88	0.75	1.36	1.53	1.39

7th hr	1.69	1.70	1.38	1.11	0.59	0.755	0.65	1.34	1.50	1.35
8th hr	1.68	1.70	1.37	0.68	0.58	0.66	0.50	1.14	1.37	1.25
9th hr	1.66	1.69	1.28	0.48	0.46	0.32	0.28	1.04	1.35	1.105
10th hr	1.63	1.52	1.15	0.30	0.28	0.28	0.90	1.04	1.23	1.03
11th hr	0.92	1.27	0.86	0.004	0.28	0.24	0.0	0.75	1.03	0.58
12th hr	0.56	0.39	0.69	0.00	0.05	0.18	0.0	0.58	0.86	0.45

**Table 3:** Percent (%) log of remaining of sustained releases Diclofenac Sodium, Paracetamol and Ibuprofen Tablets



**Figure 7:** (a) Zero order plots to ascertain release kinetics of Diclofenac Sodium, Paracetamol and Ibuprofen (b) Higuchi plots to ascertain release kinetics of Diclofenac Sodium, Paracetamol and Ibuprofen Tablets.



**Figure 8:** (a) First Order to ascertain release kinetics of Diclofenac Sodium, Paracetamol and Ibuprofen (b) Hixon-Crowell plot to ascertain release kinetics of Diclofenac Sodium, Paracetamol and Ibuprofen Tablets.

All four brands of Paracetamol SR tablets were maintained a steady state release pattern throughout the defined period i.e. 12 hours. In 12th hour sample P01, P02, P03 and P04 were released 99.00%, 98.87%, 98.48% and 99.00% of drug in phosphate buffer (pH 6.8) respectively. Three brands of Diclofenac Sodium SR tablets, all brands maintained a steady state release pattern trough out the defined period, i.e. 12 hours. In 12th hour sample D01, D02, D03 were released 96.40%, 97.57%, 95.15% of drug in phosphate buffer (pH 6.8) respectively. Another sustain release tablet is Ibuprofen SR tablets were maintained a steady state release pattern trough out the defined period, i.e. 12 hours. In 12th hour sample I01, I02, I03 were released 96.16%, 92.74%, 97.15% of drug in phosphate buffer (pH 6.8) respectively. The release rate of the samples was determined reputedly 1 hour for around 12 hours. The release rate of the diclofenac sodium, paracetamol and ibuprofen were presented in the Table 1, Table 2 and Table 3 respectively. To understand the release kinetics of sustain release tablets corresponding data were canvassed by various dissolution kinetics models such as Zero Order, First Order, Higuchi, and Hixon-Crowell etc. According to percent release vs. time (Figure 7a), the log of percent release vs. time (Figure 8a), percent release vs. square root

time (Figure 7b) and cube root of percent release vs. time respectively (Figure 8b).

## Conclusion

After completed this experiment it was observed some of the commercial paracetamol tablets were released into the dissolution medium within short period of time. The maximum percentage of released of paracetamol tablets were observed in first two hours compared with sustain release dosage forms. In 11th hour, percentage of released of diclofenac sodium were increased due to the physiochemical properties of drugs. The percentage of released of ibuprofen tablets were shown constant rate throughout the period (e.g. 12th Hour).

## Authors' Contribution

MDS and TN carried out the studies. TS and MHUS contributed in composing the article. MTI helped to draft the manuscript. MHK designed the study. All authors read and approved the final manuscript.

## Acknowledgment

We are grateful to Biopharmaceutics Laboratory, Department of Pharmacy, State University of Bangladesh for providing facilities and technical support.

## Funding

Self Funded

## Conflict of interest

We declare that we have no conflict of interest.

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