REPORT

IN VITRO DISSOLUTION STUDIES OF DIFFERENT BRANDS OF SUSTAINED RELEASE DICLOFENAC SODIUM MATRIX TABLET AVAILABLE IN BANGLADESH

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ABSTRACT

Commercially available national thirteen brands and three international brands of diclofenac sodium sustained release matrix tablets were studied in simulated gastric medium (pH 1.2) for 2 hours time period and simulated intestinal medium (pH 6.8) for 10 hours time period using USP reference dissolution apparatus. All the national and international brands complied with the USP *in-vitro* dissolution specification for drug releases in simulated gastric medium. However, four of the national brands (Code: DS-5, DS-8, DS-12, and DS-13) failed to fulfill their official requirement of 80% drug release within 8th hour in simulated intestinal medium. Drug release of those four national brands were 78.1%, 74.9%, 72.1%, and 77.8% respectively within the specified time period, however one national brand (Code: DS-2) released 83.2% drug within 6th hour in intestinal medium. Drug release profiles were analyzed for Higuchi equation, zero order, and first order to reveal the release kinetics perspective of diclofenac sodium sustained release matrix tablets. It was found that zero order release kinetics was predominant release mechanism than first order and Higuchi release kinetics for those brands (Code: DS-1, DS-3, DS-4, DS-6, DS-7, DS-9, DS-10, DS-11, DS-X, DS-Y and DS-Z) which complied with the USP *in vitro* dissolution specification for drug releases. On the other hand, first order release kinetics was predominant for five national substandard formulation brands (Code: DS-2, DS -5, DS-8, DS-12 and DS-13).

Keyword: *In-vitro* dissolution, Sustained release, Market preparations, Kinetic analysis, Diclofenac sodium, National brand, International brand.

INTRODUCTION

Diclofenac is commonly prescribed as non-steroidal anti-inflammatory substance (NSAIS) that is taken to reduce inflammation, reducing pain in conditions such as acute injury, musculoskeletal, especially to treat rheumatoid arthritis, osteoarthritis, syondyarthritis, gout attacks, pain management in case of kidney stone. It is very effective in the management of menstrual pain, ovulatory pain, acute migraines, post-operative and post-traumatic pain, female breast cancer and pain associated with bony metastases (Goodman and Gilman's, 2001). Gastrointestinal disturbances are the major adverse effect associated with diclofenac therapy (Haider *et al.*, 2001) and thus, for oral administration, the drug is usually formulated as coated tablets. Diclofenac sodium formulated for oral sustained releases dosage form, which indicated an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual release over an extended period. So this type of formulation exhibited quick on set of action and continued for prolonged period (Aulton, 1988).

The process of *in vitro* dissolution played a vital role in liberating a drug from the tablet matrix and marking whether it is available for subsequent gastrointestinal absorption. The *in vitro* dissolution of the drug from the tablet matrix depended on many factor, which include not only the physiochemical properties of drug, but also the nature of formulation and the process of manufacturing (Augsburger *et al*, 1983). Hence *in vitro* dissolution analysis of pharmaceutical dosage form has emerged a very important parameter that ensured product quality as well as for differentiating among formulations of the same therapeutic agent (Ayres *et al.*, 1984). For sustained release tablets the role of *in vitro* dissolution become still more crucial as an additional coating step involve in manufacturing process (Lordi, 1992).

In vitro dissolution study is an important tool in the evaluation of the best formulation and also in the understanding of possible risks related to specific gastrointestinal environment, dose dumping, food effects on bioavailability and interaction with other drugs (Sungthongjeen *et al.*, 1999). Today dissolution studies are the most frequently used tools in the development, characterization and utilization processes of controlled release formulations (Longer *et al.*, 1990).

In Bangladesh there are number of pharmaceutical companies manufacturing and marketing sustained release diclofenac sodium matrix tablet. Besides the national

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Table 1: Zero order release kinetic profiles of different brands national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

Time (hours)	DS-1	DS-2	DS-3	DS-4	DS-5	DS-6	DS-7	DS-8	DS-9	DS-10	DS-11	DS-12	DS-13	DS-X	DS-Y	DS-Z
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	5.3	7.1	6.9	6.4	8.9	7.1	5.2	10.9	8.9	3.9	9.2	3.8	5.6	10.2	9.4	10.7
2	9.98	12.6	10.5	10.9	14.3	12.6	10.8	16.1	14.3	7.8	17.5	12.1	15.9	19.3	19.6	20.4
3	16.1	38.5	19.3	20.1	21.3	18.3	17.9	22.9	23.6	26.4	29.8	18.2	21.1	27.9	26.9	27.7
4	27.4	47.7	30.8	29.4	34.2	31.3	28.8	31.8	33.6	34.7	35.8	22.5	24.6	36.4	35.2	37.8
5	39.8	58.2	41.3	38.7	39.6	40.3	39.1	36.9	40.2	43.9	47.1	28.9	33.1	42.3	43.9	44.1
6	48.7	68.5	50.3	47.3	46.4	48.1	49.1	41.3	47.8	51.8	56.3	37.3	35.2	50.8	51.1	51.2
7	57.5	74.9	59.1	55.8	51.8	59.9	57.1	47.8	60.1	59	62.3	45.8	41.8	58.6	60.4	57.9
8	65.8	83.2	68.1	67.2	59.3	69.1	68.7	54.6	69.4	67.3	70.6	52.1	46.9	67.9	65.3	63.8
9	78.3	84.2	76.5	75.6	64.2	77.1	74.3	60.4	75.2	71.9	78.3	57.8	56.4	76.7	73.4	71.1
10	86.2	84.6	82.2	83.7	69.3	85.1	81.9	66.7	82	80.2	83.1	62.3	64.3	82.7	81.9	80.6
11	87.4	84.6	86.5	85.7	74.3	87.1	83.5	70.1	85.2	85.1	86.9	69.2	69.7	87.6	84.3	84
12	87.4	84.6	86.7	87.2	78.1	87.1	87.1	74.9	86.1	87.7	86.9	72.1	77.8	87.7	89.2	90.1

Table 2: First order release kinetic profiles of different brands of national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

Time (hours)	DS-1	DS-2	DS-3	DS-4	DS-5	DS-6	DS-7	DS-8	DS-9	DS-10	DS-11	DS-12	DS-13	DS-X	DS-Y	DS-Z
0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
1	1.98	1.96	1.97	1.97	1.96	1.97	1.98	1.95	1.96	1.98	1.96	1.98	1.97	1.95	1.96	1.95
2	1.95	1.92	1.95	1.95	1.93	1.94	1.95	1.92	1.93	1.96	1.92	1.94	1.92	1.91	1.91	1.9
3	1.92	1.85	1.91	1.9	1.9	1.91	1.91	1.89	1.88	1.87	1.85	1.91	1.9	1.86	1.86	1.86
4	1.86	1.81	1.84	1.85	1.82	1.84	1.85	1.83	1.82	1.81	1.81	1.89	1.88	1.8	1.81	1.79
5	1.78	1.72	1.77	1.79	1.78	1.78	1.78	1.8	1.78	1.75	1.72	1.85	1.83	1.76	1.75	1.75
6	1.71	1.64	1.7	1.72	1.73	1.72	1.71	1.77	1.72	1.68	1.64	1.8	1.81	1.69	1.69	1.69
7	1.63	1.58	1.61	1.65	1.68	1.6	1.63	1.72	1.6	1.61	1.58	1.73	1.76	1.62	1.6	1.62
8	1.53	1.47	1.5	1.52	1.61	1.49	1.5	1.66	1.49	1.51	1.47	1.68	1.73	1.51	1.54	1.56
9	1.34	1.34	1.37	1.39	1.55	1.36	1.41	1.6	1.39	1.45	1.34	1.63	1.64	1.37	1.42	1.46
10	1.14	1.23	1.25	1.21	1.49	1.17	1.26	1.52	1.26	1.3	1.23	1.58	1.55	1.24	1.26	1.29
11	1.1	1.12	1.13	1.16	1.41	1.11	1.22	1.48	1.17	1.17	1.12	1.49	1.48	1.09	1.2	1.2
12	1.1	1.12	1.12	1.11	1.34	1.11	1.11	1.4	1.14	1.09	1.12	1.45	1.35	1.09	1.03	1

brands there are few international brands also available in drug stores. This paper deals with the comparative *in vitro* dissolution or *in vitro* bioavailability characteristic of sustained release matrix tablets of most commonly available national and international brands of diclofenac sodium in Bangladesh.

MATERIAL AND METHOD

Chemicals: USP references standard of Diclofenac Sodium (Merk, Germany). *Reagents:* Hydrochloric acid (Merk, Germany); Sodium Hydroxide (Merk, Germany); Ortho-phosphoric acid (Merk, Germany). *Equipments:* Simadzu UV spectophometer; Digital pH meter; Electrolab Tablet Dissolution Test machine (XXII); Sartorius electronic balance.

Dosages forms

Thirteen national and three international brands of marketed (production date not more than four month ago from the time of purchase) diclofenac sodium sustained releases matrix tablets of the test drug were obtained from various stores. The samples were properly checked for their manufacturing license number, batch number, and date of manufacture and expiry dates before purchasing. They were randomly coded (DS-1, DS-, DS-2, DS-3, DS-4, DS-5, DS-6, DS-7, DS-8, DS-9, DS-10, DS-11, DS-12, DS-13) for national brands and (DS-X, DS-Y, DS-Z) for international brands. The labeled active ingredient contain diclofenac sodium were 100mg and packaged in strip or in blister packing. The strip or blister packs stored at 25±2°C for four weeks before the dissolution study in order to evaluate any organoleptic changes.

Table 3: Higuchi release kinetic profiles of different brands of national and international sustained release diclofenac sodium matrix tablets available in Bangladesh Pharma market

SQRT	DS-1	DS-2	DS-3	DS-4	DS-5	DS-6	DS-7	DS-8	DS-9	DS-10	DS-11	DS-12	DS-13	DS-X	DS-Y	DS-Z
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	5.3	7.1	6.9	6.4	8.9	7.1	5.2	10.9	8.9	3.9	9.2	3.8	5.6	10.2	9.4	10.7
1.4	9.98	12.6	10.5	10.9	14.3	12.6	10.8	16.1	14.3	7.8	17.5	12.1	15.9	19.3	19.6	20.4
1.7	16.1	38.5	19.3	20.1	21.3	18.3	17.9	22.9	23.6	26.4	29.8	18.2	21.1	27.9	26.9	27.7
2	27.4	47.7	30.8	29.4	34.2	31.3	28.8	31.8	33.6	34.7	35.8	22.5	24.6	36.4	35.2	37.8
2.2	39.8	58.2	41.3	38.7	39.6	40.3	39.1	36.9	40.2	43.9	47.1	28.9	33.1	42.3	43.9	44.1
2.4	48.7	68.5	50.3	47.3	46.4	48.1	49.1	41.3	47.8	51.8	56.3	37.3	35.2	50.8	51.1	51.2
2.6	57.5	74.9	59.1	55.8	51.8	59.9	57.1	47.8	60.1	59	62.3	45.8	41.8	58.6	60.4	57.9
2.8	65.8	83.2	68.1	67.2	59.3	69.1	68.7	54.6	69.4	67.3	70.6	52.1	46.9	67.9	65.3	63.8
3	78.3	84.2	76.5	75.6	64.2	77.1	74.3	60.4	75.2	71.9	78.3	57.8	56.4	76.7	73.4	71.1
3.2	86.2	84.6	82.2	83.7	69.3	85.1	81.9	66.7	82	80.2	83.1	62.3	64.3	82.7	81.9	80.6
3.32	87.4	84.6	86.5	85.7	74.3	87.1	83.5	70.1	85.2	85.1	86.9	69.2	69.7	87.6	84.3	84
3.5	87.4	84.6	86.7	87.2	78.1	87.1	87.1	74.9	86.1	87.7	86.9	72.1	77.8	87.7	89.2	90.1

Table 4: Drug release mechanisms (Multiple coefficient [r^2]) of different brands of national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

Code	Multiple coefficient of determination		
	Zero order	First order	Higuchi
DS- 1	0.9780	0.8930	0.8267
DS-2	0.8584	0.9464	0.8977
DS- 3	0.9833	0.9269	0.8558
DS- 4	0.9865	0.9105	0.8474
DS-5	0.8822	0.9789	0.9125
DS- 6	0.9823	0.9142	0.8524
DS- 7	0.9836	0.9252	0.8453
DS-8	0.8835	0.9788	0.9254
DS- 9	0.9846	0.9387	0.8824
DS- 10	0.9809	0.9387	0.8721
DS- 11	0.9697	0.9590	0.9158
DS-12	0.8949	0.9563	0.8559
DS-13	0.8730	0.9139	0.8649
DS-X	0.9839	0.9331	0.9106
DS-Y	0.9862	0.9353	0.9142
DS-Z	0.9844	0.9203	0.9246

Dissolution study

These studies were conducted at 37±0.5°C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six section assembly according to the USP XXIII procedure with minor modification (USP XXII and NF XVII, 1995).

For *in vitro* dissolution studies simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 6.8) were required.

a) *Preparation of simulated gastric medium* (0.1 N HCl pH 1.2)

For 0.1N HCl, 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml.

b) *Preparation of simulated intestinal medium* (Buffer pH 6.8)

20 ml Sodium Hydroxide (25%) was diluted with 0.1 N Hydrochloric acid to 1000 ml adjusting pH 6.8 by addition of 1.2 ml *O*-phosphoric acid. The dissolution test was performed using 900 ml medium at 37±0.5°C and 50 rpm.

The medium was preheated to 37°C and then added to the vessels after the medium was placed in the vessels, paddle rotation was started and the system was allowed to equilibrate for 15 min. Each vessel, vessel position, and corresponding tablet result were assigned the same number. Thus, for each sub sample of six tablets tested

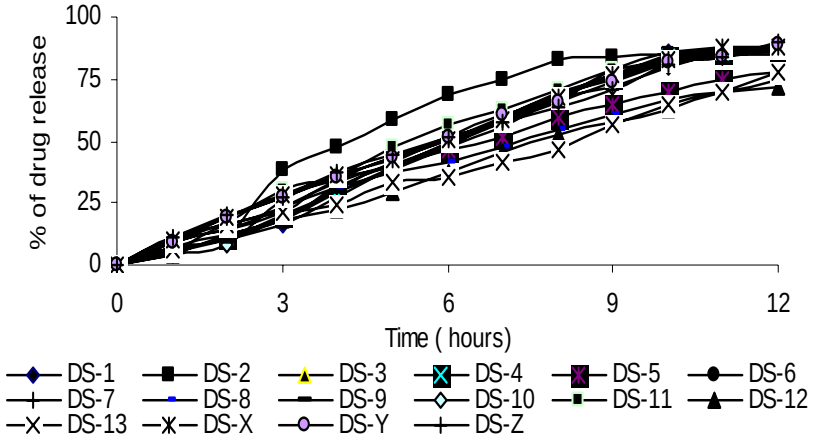

Fig. 1: Zero order release kinetic of different brands of national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

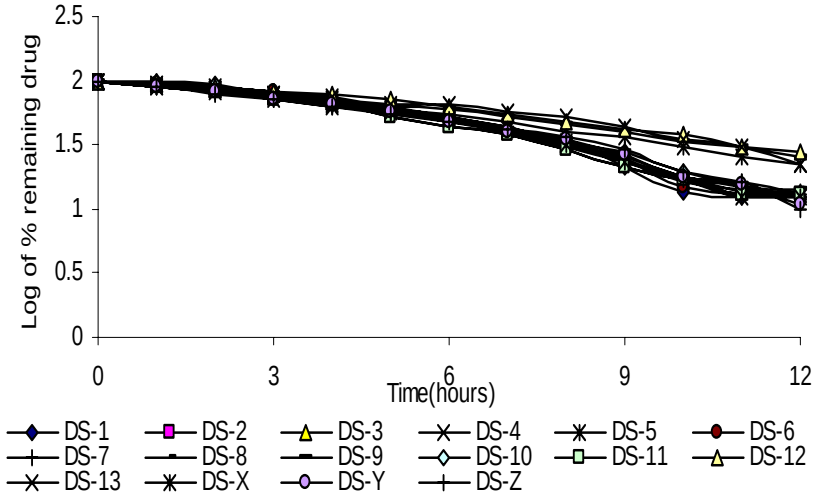

Fig. 2: First order release kinetic of different brands of national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

simultaneously, every individual tablet result was identified with a particular vessel and position.

The total duration of dissolution was 12 hours in which the first 2 hours the tablet matrices were subjected to simulated gastric media (0.1N HCl pH 1.3) and the later 10 hours the tablet matrices were subjected to simulated intestinal media (Buffer pH 6.8).

Acid stage

900 ml of 0.1N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 277 nm.

Buffer stage

After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ±0.05) was adjusted with addition of 1.2 ml *O*-phosphoric acid. The operation was continued for 10 hours.

At every one-hour interval sample (10 ml) of the solution was withdrawn from the dissolution medium and immediately replaced with equal volumes of dissolution medium.

The withdrawn samples (10ml) was then filtered and diluted, analyzed at 277nm for diclofenac sodium by UV spectrophotometer (Shimadzu, Model UV-160A, Kyoto, Japan). The amounts of drug present in the samples were calculated from calibration curves constructed from the standard solution of USP reference standard test drugs.

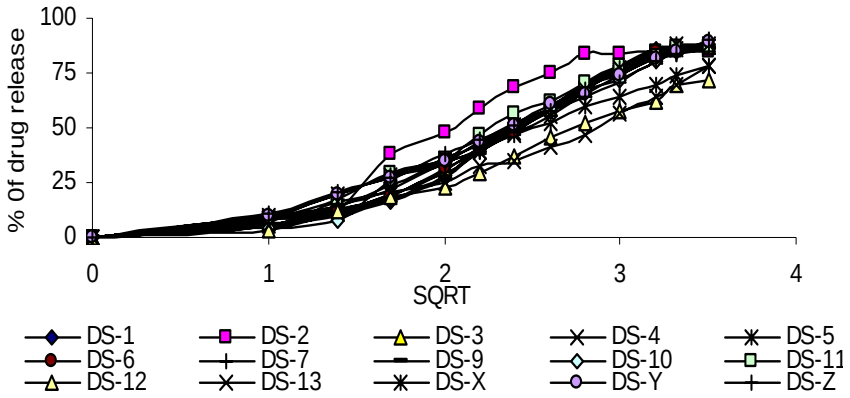

Fig. 3: Higuchi release kinetic of different brands of national and international sustained release diclofenac sodium matrix tablets commercially available in Bangladesh Pharma market

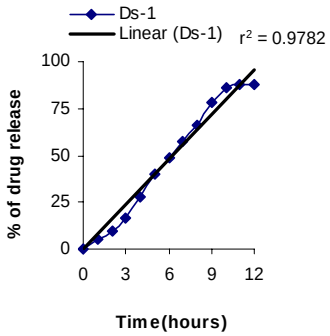

Fig. 4.1: Best fit figure for DS-1 drug release mechanism

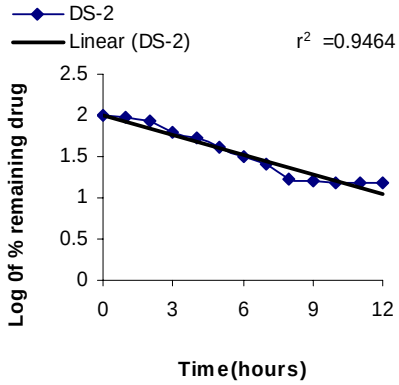

Fig. 4.2: Best fit figure for DS-2 drug release mechanism

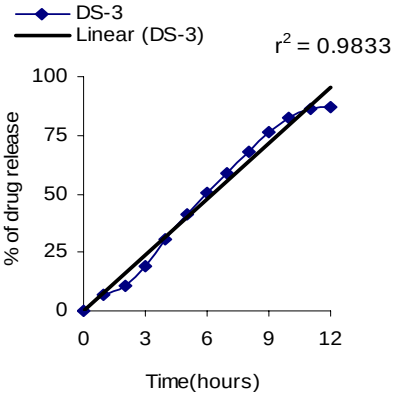

Fig. 4.3: Best fit figure for DS-3 drug release mechanism

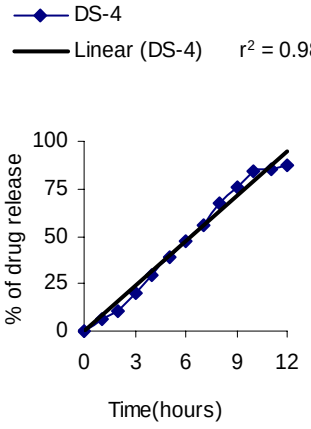

Fig. 4.4: Best fit figure for DS-4 drug release mechanism

RESULT AND DISCUSSION

Commercially available national thirteen brands (Code: DS-1, DS-3, DS-4, DS-6, DS-7, DS-9, DS-10 and DS-11), and three international brands (Code: DS-X, DS-Y and DS-Z) of diclofenac sodium SR tablets were studied for their *in vitro* dissolution behavior in simulated gastric medium (pH 1.2) for 2 hours time period and in simulated intestinal medium (pH 6.8) for 10 hours time period using USP reference dissolution apparatus and show release kinetics of the matrix tablets (table 1 and figs. 1-3). All the national and international brands complied with the

USP *in vitro* dissolution specification 25% drug release within 2 hours in simulated gastric medium. After a comprehensive *in vitro* dissolution study, it denoted that the eight national brands (Code: DS-1, DS-3, DS-4, DS-6, DS-7, DS-9, DS-10 and DS-11) and three international brands (Code: DS-X, DS-Y, DS-Z) were fulfill the USP *in vitro* dissolution specification 80% drug release within 8th hours in simulated intestinal medium. Due to substandard formulations, four of the national brands (Code: DS-5, DS-8, DS-12, and DS-13) were failed to fulfill the USP *in vitro* dissolution specification i.e., 80% drug release within 8th hours in simulated intestinal medium and one national brand (Code: DS-2) released 80% drug within 6th hours in the simulated intestinal medium. The amount of drug present in each tablet was determined by spectroscopic method and all the brands met the official standard (table 2).

The drug release mechanism was determined by multiple coefficients (r^2) for each individual brands (table 3). A zero order release kinetics was predominant than the first order and Higuchi release kinetics for the national eight brands (Code: DS-1, DS-3, DS-4, DS-6, DS-7, DS-9, DS-10 and DS-11) and three international brands (Code: DS-

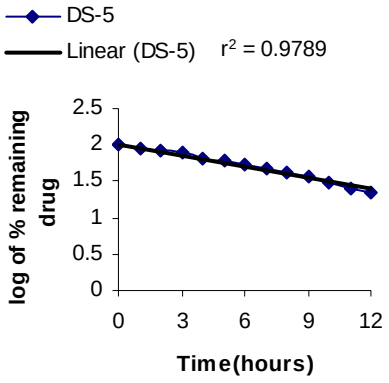

Fig. 4.5: Best fit figure for DS-5 drug release mechanism

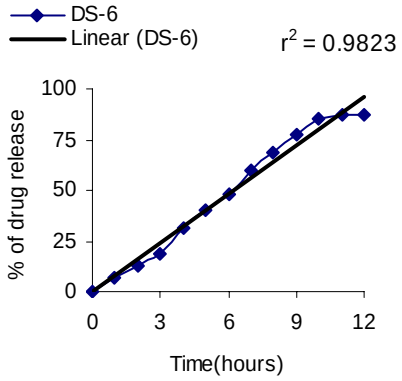

Fig. 4.6: Best fit figure for DS-6 drug release mechanism

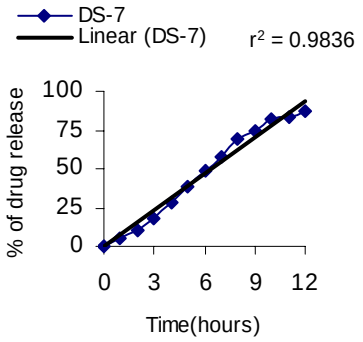

Fig. 4.7: Best fit figure for DS-7 drug release mechanism

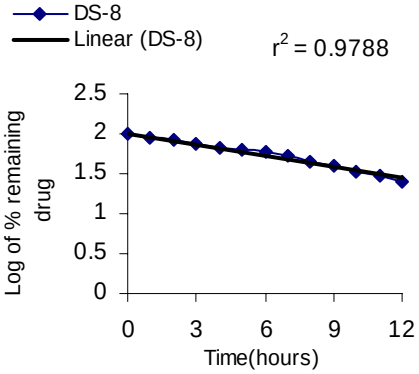

Fig. 4.8: Best fit figure for DS-8 drug release mechanism

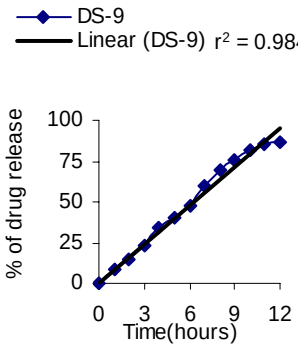

Fig. 4.9: Best fit figure for DS-9 drug release mechanism

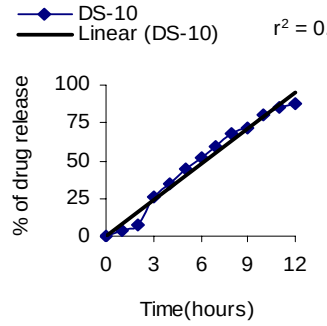

Fig. 4.10: Best fit figure for DS-10 drug release mechanism

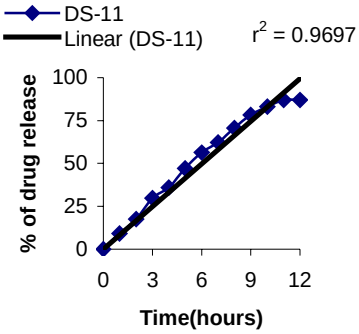

Fig. 4.11: Best fit figure for DS-11 drug release mechanism

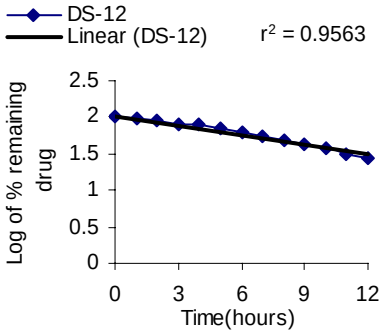

Fig. 4.12: Best fit figure for DS-12 drug release mechanism

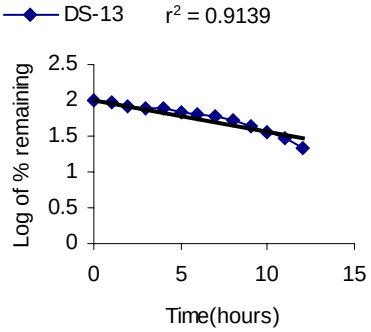

Fig. 4.13: Best fit figure for DS-13 drug release mechanism

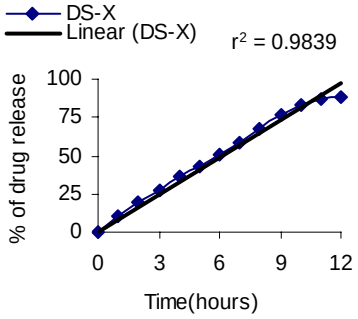

Fig. 4.14: Best fit figure for DS-X drug release mechanism

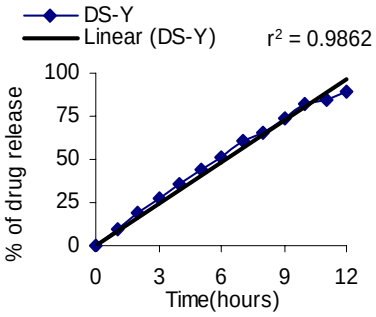

Fig. 4.15: Best fit figure for DS-Y drug release mechanism

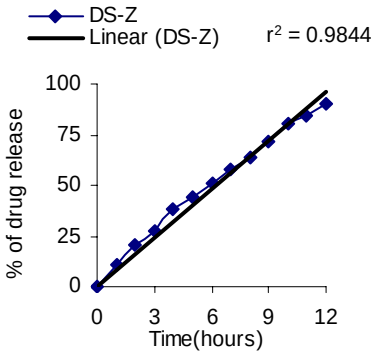

Fig. 4.16: Best fit figure for DS-Z drug release mechanism

X, DS-Y, DS-Z) respectively. It was focused that the drug release of those brands followed diffusion method and concentration independent from the matrix of tablet. First order release was predominant than the zero order and Higuchi release kinetics for the five national substandard brands (Code: DS-2, DS-5, DS-8, DS-12 and DS-13) respectively.

CONCLUSION

It is revealed that most of the commercially available brands of the diclofenac SR tablets in Bangladesh met the official specification and few of them failed which might have some formulation problems. The study also emphasized the need of constant surveillance on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for the patients in Bangladesh.

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