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EFFECT OF FRUIT JUICE ON THE DISSOLUTION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

In vitro dissolution of ten brands of diclofenac sodium sustained release matrix tablets were studied to determine the effect of fruit juice in the bioavailability of diclofenac. Significant reduction was observed in the release rate at all collected brands, where except sample D7 and D8 others were not fulfill the USP *in vitro* dissolution specification when administered with fruit juice. Therefore to avoid drug therapeutic failures and of the drug in the systemic circulation, ingestion of the juice with diclofenac sodium should be discouraged.

INTRODUCTION: Diclofenac is commonly prescribed as non-steroidal anti-inflammatory agent (NSAIA) 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 [1].

Gastrointestinal disturbances are the major adverse effect associated with diclofenac therapy [2] 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 onset of action and continued for prolonged period [3].

Literature survey suggested that a number of drugs interact with different food materials, fruit juice, dairy products and minerals supplements [4]. Fruit juice interact with many drugs, which includes, triazolam, midazolam, diazepam, alprazolam, quazepam, ritonavir, sertraline, atorvastatin, lovastatin, simvastatin, felodipine, nicardipine, difedipine, nisoldipine, nitrendipine, losartan, dextromethorphan, repaglinide, verapamil, buspirone, amiodarone, dronedarone, quinidine, disopyramide, propafenone, carvedilol, terfenadine, cisapride, sildenafil, tadalafil, vardenafil, ergotamine, nimodipine, fluvoxamine, codeine, tramadol, cyclosporine, omeprazole, zolpidem, oxycodone, hydrocodone, dihydrocodeine, methadone, trazodone, praziquantel albendazole, mebendazole, carbamazepine, imatinib, Loperamide etc [5-14].

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, the process of manufacturing and environment of gastrointestinal tract [15].

In vitro dissolution study is an important tool in the evaluation of the best formulation and also in the understanding of possible interactions related to specific gastrointestinal environment, dose dumping, food effects on bioavailability and interaction with other drugs [16].

It is common for patients to take drugs with drinks other than water for various reasons, one of which is to mask the unpleasant taste already associated with some drugs and secondly, fruit juice is often part of the menu for breakfast in some homes when medications are taken.

Moreover, it's also being used to administer drugs to children for better compliance. Some of these drinks include fruit juice, milk, beverages and yogurt. In Bangladesh there are number of pharmaceutical companies manufacturing and marketing sustained release diclofenac sodium matrix tablet which are very widely used. This study was therefore carried out to determine if the *in vitro* dissolution release and *in vitro* bioavailability characteristic of most commonly available sustained release matrix tablets of diclofenac sodium would be altered when administered with fruit juice.

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: Helios UV spectophometer (England); Digital pH meter; Tablet Dissolution Test machine (XXII) (Germany); Mettler electronic balance (Switzerland).

Dosages Forms: Ten brands of marketed (production date not more than three month ago from the time of purchase) diclofenac sodium sustained releases matrix tablets of the test drug were obtained from various drug 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, such as D1, D2, D3, D4, D5, D6, D7, D8, D9 and D10. 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 [17]. The experiment was conducted from September 2010 to February 2011.

Dissolution Testing: *In vitro* dissolution was studied by using US Pharmacopoeia dissolution apparatus II. The apparatus II was maintained at 37±0.5^{o}C with a degree of agitation of 50revolution/minute and 900ml of dissolution medium per vessel was used. The dissolution experiment was conducted in two phases; one involved the dissolution of 100mg diclofenac sodium matrix tablet using buffer dissolution medium while the other contained equal 450mls of buffer and fruit juice. For *in vitro* dissolution studies simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 6.8) were required[18].

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 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 simultaneously, every individual tablet result was identified with a particular vessel and position. At every one-hour interval sample (5ml) of the solution was withdrawn from the dissolution medium and immediately replaced with equal volumes of dissolution medium. The withdrawn samples (5ml) were then filtered and diluted, analyzed at 277nm for diclofenac sodium by UV spectrophotometer.

The amounts of drug present in the samples were calculated from calibration curves constructed from the standard solution of USP reference standard diclofenac sodium.

The total duration of dissolution was 12 hours in which the first 2 hours tablet matrices were subjected to simulated gastric media (0.1N HCl pH 1.2) and the later 10 hours the tablet matrices were subjected to simulated intestinal media (Buffer pH 6.8).

RESULTS AND DISCUSSION: Commercially available ten brands of diclofenac sodium sustained release matrix tablets were studied for their *in vitro* dissolution behavior in two phases; one using buffer dissolution medium while the other contained equal volume of buffer dissolution medium and fruit juice. Release rate of the samples were determined hourly for 12 hours where first 2 hours in simulated gastric media and later 10 hours in simulated intestinal media. Results of sample D1 to D5 and sample D6 to D10 were presented in the **table 1, 2 and figure 1** respectively.

TABLE 1: RELEASE PROFILES OF SAMPLE D1 – D5 IN TWO PHASES- A) IN BUFFER DISSOLUTION MEDIUM AND B) IN EQUAL 450ml OF BUFFER AND FRUIT JUICE

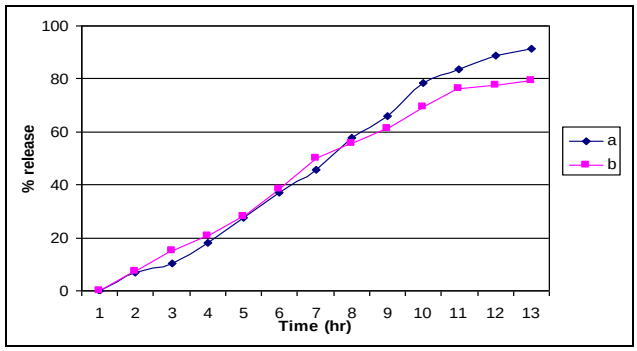
Time (hours)	% of Release									
	D1		D2		D3		D4		D5	
	a	b	a	b	a	b	a	b	a	b
0	0	0	0	0	0	0	0	0	0	0
1	6.9	7.4	5.4	6.3	5.9	7.1	7.3	8.1	9.8	7.8
2	10.2	15.3	9.4	11.1	10.4	12.3	12.2	16.6	17.5	16.2
3	17.9	20.9	16.3	20.8	19.3	22.6	20.4	23.8	27.7	24.3
4	27.4	27.9	24.2	27.5	30.2	28.3	28.1	35.4	35.4	33.3
5	36.9	38.4	35.2	36.8	41.6	37.4	40.7	43.7	48.2	41.2
6	45.9	50.1	41.4	44.7	50.3	44.7	47.3	51.1	56.2	48.9
7	57.6	55.7	51.8	49.2	60.6	53.8	57.8	56.3	65.3	59.4
8	65.9	61.3	58.1	57.6	70.4	59.6	68.7	61.2	72.3	66.4
9	78.4	69.5	74.8	63.8	79.7	67.3	83.9	69.6	86.1	71.8
10	83.7	76.2	82.2	69.4	86.2	71.5	88.4	72.4	90.2	77.2
11	88.6	77.4	89.8	77.7	88.1	74.3	91.1	78.9	93.2	81.6
12	91.5	79.1	94.4	83.3	89.3	76.1	96.4	81.3	96.5	82.1

a = Dissolution in buffer medium; b = Dissolution in buffer medium + fruit juice

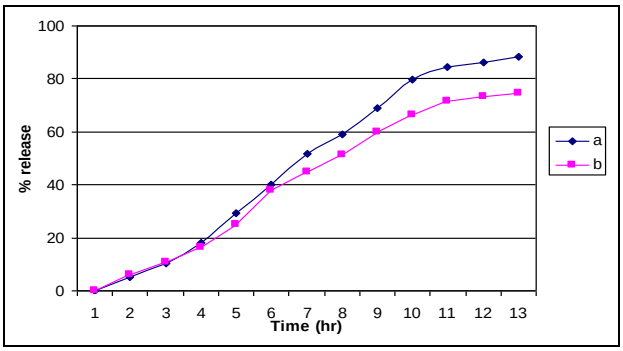
TABLE 2: RELEASE PROFILES OF SAMPLE D6 – D10 IN TWO PHASES- A) IN BUFFER DISSOLUTION MEDIUM AND B) IN EQUAL 450ml OF BUFFER AND FRUIT JUICE

Time (hours)	% of Release									
	D6		D7		D8		D9		D10	
	a	b	a	b	a	b	a	b	a	b
0	0	0	0	0	0	0	0	0	0	0
1	5.3	5.9	10.1	9.4	9.8	5.3	9.4	5.9	8.3	9.1
2	10.4	10.8	23.8	17.3	19.3	10.4	19.7	10.8	14.1	13.8
3	18.1	16.3	33.3	28.6	28.5	18.1	27.6	16.3	22.1	19.1
4	29.5	24.8	43.2	37.3	41.5	29.5	38.4	24.8	33.6	26.8
5	40.1	37.9	56.5	48.7	53.1	40.1	49.8	37.9	40.2	34.7
6	51.8	44.7	65.4	55.9	59.4	51.8	63.7	44.7	48.1	45.2
7	59.2	51.2	71.6	64.3	64.7	59.2	72.8	51.2	57.2	55.1
8	69.1	59.9	85.2	70.5	72.2	69.1	86.7	59.9	66.8	63.9
9	79.8	66.4	94.2	79.8	87.8	79.8	92.4	66.4	88.2	74.6
10	84.5	71.4	95.1	83.2	90.2	84.5	95.9	71.4	89.2	79.3
11	86.2	73.4	96.9	84.6	92.1	86.2	96.2	73.4	90.3	82.5
12	88.2	74.4	97.6	84.9	92.9	88.2	96.9	74.4	91.7	83.1

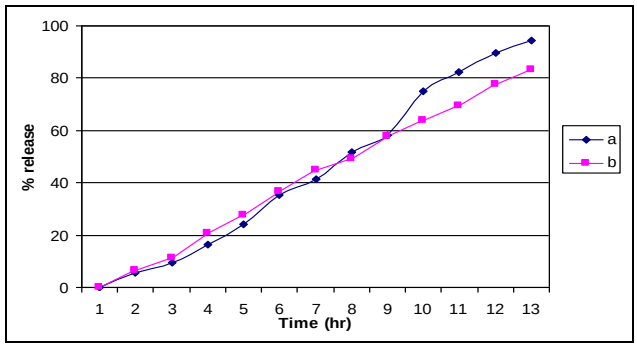
a = Dissolution in buffer medium; b = Dissolution in buffer medium + fruit juice



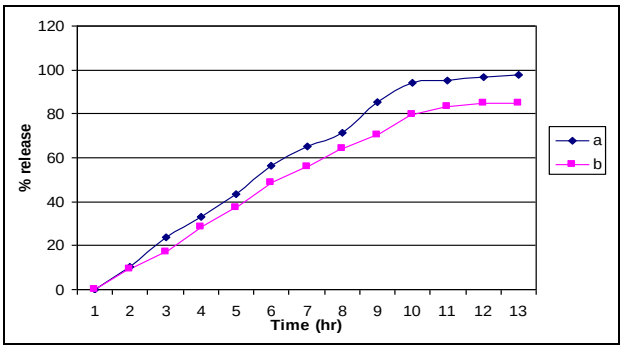
SAMPLE D1



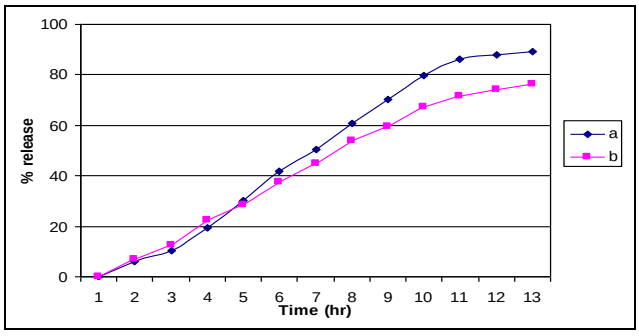
SAMPLE D6



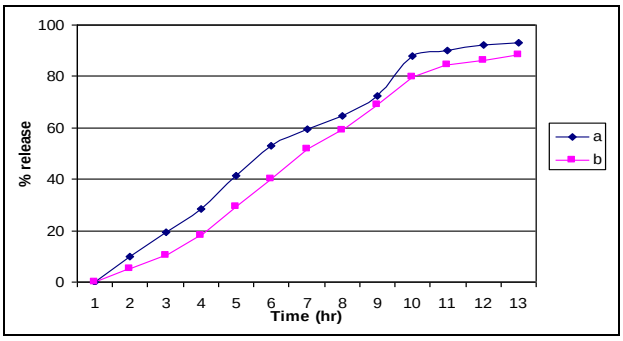
SAMPLE D2



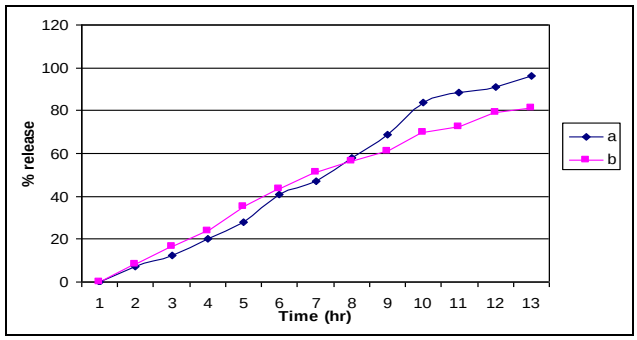
SAMPLE D7



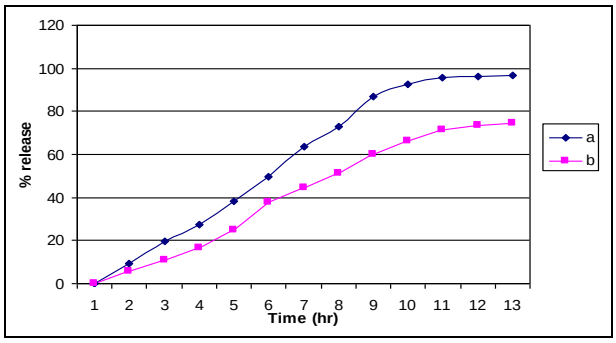
SAMPLE D3



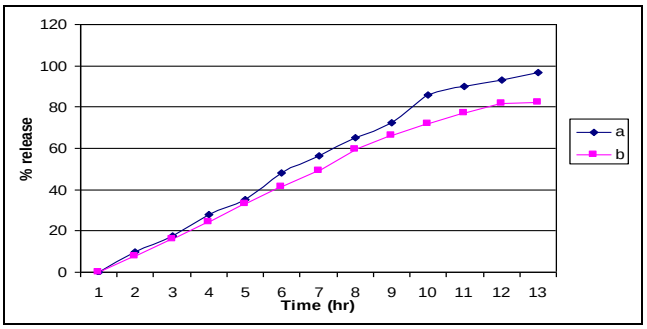
SAMPLE D8



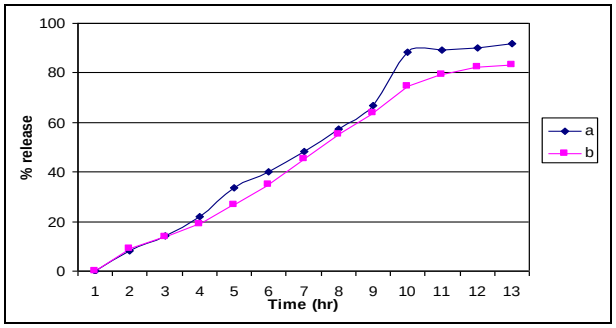
SAMPLE D4



SAMPLE D9



SAMPLE D5



SAMPLE D10

FIG. 1: RELEASE PROFILES OF 10 BRANDS OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS IN TWO PHASES- A) IN BUFFER DISSOLUTION MEDIUM AND B) IN EQUAL 450MLS OF BUFFER AND FRUIT JUICE

After a comprehensive *in vitro* dissolution study in two different phases, it denoted that the initial release rate of 04 brands (Code: D5, D7, D8 and D9) were faster in medium containing fruit juice. But after 3 to 7 hours the absolute reduction of diclofenac release in the fruit juice was observed which might be an indication of interaction between the drug and the components of fruit juice. In dissolution media, all the brands were fulfill the USP *in vitro* dissolution specification i.e., 80% drug release within 8th hours in simulated intestinal medium, but only 02 brands (Code: D7 and D8) were fulfill the specification in presence of fruit juice.

After 12 hours, 04 brands (Code: D1, D3, D6 and D9) released less than 80% of drug in presence of fruit juice, where except 01 brand (Code: D8), the other brands (Code: D2, D4, D5, D7 and D10) were fulfill the specification i.e., 80% drug release within 10th hours very marginally. Sample D8 released 84.5% of drugs at 10th hour in fruit juice.

CONCLUSION: This study was carried out to determine the alteration of *in vitro* dissolution release and *in vitro* bioavailability characteristic of diclofenac sodium sustained release matrix tablets when administered with fruit juice. The study revealed that all ten collected brands of diclofenac sodium matrix tablets showed significant reduction of release rate which might be the indication of interaction between the drug and the components of fruit juice.

By way of conclusion, we have confirmed that concomitant administration of diclofenac sodium in the presence of fruit juice still lead to reduction of bioavailability. The phenomenal increase in bioavailability of drug co-administered with fruit juice was not noticed. Therefore, the incessant habit of swallowing drug with fluids other than water should be done with great caution.

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