In Vitro Dissolution Interference Study in Presence of Paracetamol Tablets with Freshly Prepared Mango Juices on Simulated Gastrointestinal Digestion

Md. Didaruzzaman Sohel[1,2,*], Faisal Asif[1], Md. Helal Uddin Sumon[3], Kaniz Fatema[1] and Md. Hassan Kawsar[1]

[1]*Biopharmaceutical Research Laboratory, Department of Pharmacy, State University of Bangladesh, Dhaka-1205, Bangladesh*

[2]*Quality Assurance Department, Incepta Pharmaceuticals Ltd., Dhaka-1341, Bangladesh*

[3]*Quality Assurance Department, NIPRO JMI Pharma Ltd. Rajendrapur, Chauddagram, Comilla, Bangladesh*

Abstract: This study is performed beneath *In Vitro* dissolution applying various mathematical approaches to observe the dissolution interference on simulated gastrointestinal digestion. In total, eight medicine samples were collected in Bangladeshi market and the conventional approaches were followed to measure the result in gastric medium (pH 1.2). Altogether, the brands showed sensibly upper dissolution discharge; primarily P01 (98.9%), P08 (98.97%), P03 (98.32%) and P06 (98.24%) were released relatively faster than the other sample in 15 to 60 minutes. Along with the mango juice in the simulated gastric medium, the brands showed sensibly upper dissolution discharge; primarily P01 (98.83%), P07 (98.98%), P06 (98.78%) and P03 (98.38%) were released relatively faster than the other sample in 15 to 60 minutes. This result depicts to understand the proper release of kinetics with the help of various mathematical model such as Zero order, First order, Higuchi and Hixson-Crowell model etc. although Paracetamol can interact with the fruit juices, which may alter the drug release, drug absorption in the body and may also lead to an unwanted reaction.

Keywords: Paracetamol, Drug Interactions, Mango Juice, Bangladesh.

1. INTRODUCTION

Paracetamol is a widespread over-the-counter (OTC) drug, also recognized as acetaminophen or N-acetyl-p-aminophenol, used as a centrally interim pain-relieving and antipyretic medication [1, 2]. Food and Agriculture Organization (FAO) and World Health Organization (WHO) suggest an everyday dietary intake of around five servings or 400 g of vegetables and fruits to support in the avoidance of prolonged diseases for example cancer, diabetes, cardiac disease and obesity etc. For this instance, there is an augmented worldwide consumer mandate for vegetables and fruits [3]. The vegetables and fruits may interrupt the pharmacodynamics and pharmacokinetics of potential drug-food interactions including the drugs that have a narrow therapeutic window [4]. In this study, freshly prepared mango juice including mango pulp and paracetamol medication were used as the fruit and drug, respectively, for the drug-fruit interaction study. Mango and its components are widely popular for using as daily dietary cuisine mainly in The Southern Asian region including Bangladesh [5]. A Study on the basis of *In vitro* dissolution represented crucial purpose in emancipating the medicine from the tablet matrix and design for resulting gastrointestinal absorption. The purpose for expending freshly prepared mango juices including pulp was because of the presence of a huge number of bioactive ancillary metabolites such as cardenolides alkaloids, tannins, saponins, flavonoid, and anthocyanins some of which have been shown to inhibit the activity of CYP isoenzymes constituents that have the prospectively effect on the transportation and metabolism of some medicine [6, 7]. Paracetamol, with assistance of cytochrome P450 enzymes, transport and metabolize the drug in the systemic circulation. However, grapefruit, papaya, orange mango and its components hinder P450 enzymes of human [8, 9]. So, this study focuses on the paracetamol hindrance time in the presence of freshly prepared fruit juice specifically mango juice, along with pulp, from the primary drug release condition to the next sixty min time by applying *In vitro* dissolution approaches in simulated gastrointestinal digestion. To understand the release and interaction, different mathematical models are approached mainly Zero order, First order, Higuchi and Hixson-Crowell model etc.

2. MATERIALS AND METHODS

Analytical grade instruments and reagents that were used for dissolution studies of Standard Paracetamol

*Address correspondence to Md. Didaruzzaman Sohel, Quality Assurance Department, Incepta Pharmaceuticals Ltd., Dhaka-1341, Bangladesh;
E-mail: sohelphr15@gmail.com, didaruzzaman@inceptapharma.com

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sample (99.8% potency) were collected from Incepta Pharmaceuticals Ltd, Dhaka.

2.1. Apparatuses

A Dual beam Shimadzu UV-visible spectrometer (UV mini-1700, Shimadzu Corporation, Kyoto, Japan with 1 cm quartz cells). HANNA HI 2211 pH meter (Romania), automatic tablet dissolution tester with eight-basket system UDA-80 USP Standard (Veego, India).

2.2. Samples Collection

Randomly selected Top eight Paracetamol tablets (manufacturing date was not more than three month ago from the period of procurement) from various drug stores. Manufacturing license number, group number, and time of production and expiry times before procuring were properly checked. Their proper codes were also obtained, such as P01, P02, P03, P04, P05, P06, P07 and P08. The considered active components of paracetamol were 500 mg and they were packed in groups 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.

2.3. The Formulation of the Selected Sample

The claimed average formulary ingredients of the selected paracetamol 08 tablets are listed below:

Paracetamol BP or USP (500.00±3.0 mg), Maize Starch BP (70.50±0.18 mg), Poly vinyl pyrrolidone BP (3.00±0.80 mg), Methyl paraben sodium BP (0.50±0.07 mg), Propyl paraben sodium BP (0.05±0.02mg) Sodium starch glycolate BP (5.5±0.25 mg), Magnesium stearate BP or USP (2.00±0.15 mg), Purified Talc BP or Pharma grade (5.00±03 mg).

The claimed average of coating material of the 08 paracetamol tablets are mentioned below:

Hydroxy propyl methyl cellulose (HPMC) BP or USP (4.00±0.30 mg), Titanium dioxide BP (1.00±0.40 mg), Purified Talc BP (1.50±0.50 mg), Isopropyl alcohol BP or Ph. Grade (60.00±2.5 mg), Methylene chloride BP or Ph. Grade (70.00±0.25 mg), PEG-6000 BP (1.00±0.30 mg).

The claimed dissolution (% Drug) of the 08 paracetamol tablets as below:

After 10 min:

P01 (70.78%), P02 (70.50%, P03 (68.00 %), P04 (72.50 %), P05 (75.00%), P06 (77.00 %), P07 (73.50%) and P08 (85.00 %).

After 20 min:

P01 (75.63%), P02 (81.73%), P03 (77.26 %), P04 (88.29 %), P05 (88.35%), P06 (83.64 %), P07 (89.33%) and P08 (90.23 %).

After 30 min:

P01 (85.28%), P02 (88.17%), P03 (93.23%), P04 (95.49 %), P05 (94.25%), P06 (92.42 %), P07 (95.38%) and P08 (94.00 %).

2.4. Standard Solution Preparation

100 mg Paracetamol powder (99.8% pure) was taken in a 100 ml volumetric flask and added with 10 ml of 0.1N NaOH.

2.5. In Vitro Dissolution Study

The apparatus was maintained at 37±0.5°C with a grade of agitation of 50 revolution/minute and 900 ml of dissolution medium per vessel was applied. The experimentation was conducted in two stages. Firstly, apply the 500 mg Paracetamol tablet employing buffer dissolute on the medium. Secondly, 700 ml of buffer and 200 ml of freshly prepared mango juice pulp weree added for the dissolution study. For the performance of *in vitro* dissolution examination, simulated gastric medium (pH 1.2) is mandatory [10].

2.6. Preparation of Simulated Gastrointestinal Condition

To prepare the Chloride Buffer pH 2.0 (0.1 N HCl; pH 2.0), dissolve 6.57g KCl in water, add 119 ml of 0.1N HCl and dilute to 1000ml water for the simulated gastrointestinal condition [11, 12].

Presentation of mathematical models for drug release.

2.7. Zero Order Release

The drug rate constant and the drug initial concentration data is expressed by zero-order rate equations. The mathematical representation of zero order release equation is

$[A]_t = K_0 t + [A]_0$

Where $[A]_t$ refers cumulative amount of drug release at time "t", t refers to time in hours, $[A]_0$ refers to initial quantity of the drug and K_0 t refers to the zero order release constant [13].

2.8. First Order Release

The first order release rate is straightly proportional to the concentration of the reactants. The first-order reaction equation is:

$\text{Log } [A]_t = \text{Log } [A]_0 + K_t /2.303$

Where $[A]_t$ refers to cumulative amount of drug release at time "t", t refers to time in hours, $[A]_0$ refers to the initial quantity of the drug and K_0 t refers to the zero order release constant [14].

2.9. Higuchi Model

The Higuchi equation is considered as one of the widely used and the most recognized controlled-release equations. The Higuchi equation is

$[A] = K_H t^{1/2}$

Where [A] refers to cumulative amount of drug released at time t, K_H is the Higuchi constant and t refers to time in hours [15].

2.10. Hixson-Crowell Model

The Hixson-Crowell cube root law defines the release from dissolution medium where there is a transformation in the surface part and diameter of particles or tablets

$[A]_0^{1/3} - [A]_t^{1/3} = K_{HC}{}^t$

Where $[A]_0$ refers to the initial quantity of the drug, $[A]_t$ refers to cumulative amount of drug release at time "t", KHC is the Hixson-crowell constant describing the surface volume relation and t refers to time in hours [16].

3. RESULT AND DISCUSSION

The core purpose of the study is to focus on solution 0.01 to 0.05 mg/ml for calculating standard curve of Paracetamol. The consistent reversion data indicated functional linear relationship R^2 = 0.998 (as measured). Eight Paracetamol tablets justifying *in vitro* dissolution behavior where the buffer dissolution medium delimited equivalent bulk of buffer closure medium with mango juice. The proclamation rate of the illustrations was determined apparently 5 minutes for specifically 60 minutes. P01 to P08 are presented in the Tables **1** and **2**, respectively. To comprehend the release kinetics medium with Mango juice closure, consistent data are applied by various dissolution

Table 1: Percent of Release Sample P01 to P08 Gastric Dissolution Medium and in Presence of Mango Juice

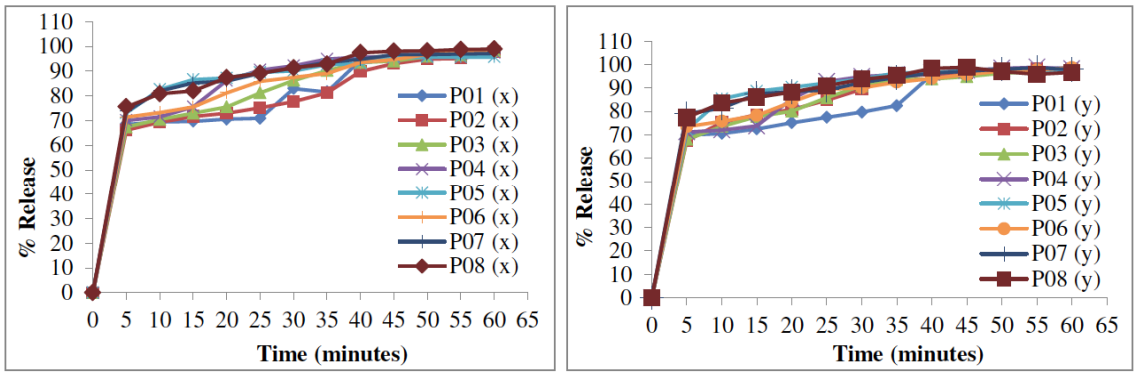
	% of Release															
Time (min)	P01 (x)	P01 (y)	P02 (x)	P02 (y)	P03 (x)	P03 (y)	P04 (x)	P04 (y)	P05 (x)	P05 (y)	P06 (x)	P06 (y)	P07 (x)	P07 (y)	P08 (x)	P08 (y)
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	68.49	69.93	66.23	67.48	67.42	68.11	70.1	71.21	73.11	72.22	71.39	73.55	73.75	78.99	75.58	77.44
10	69.46	70.62	69.35	75.32	70.53	73.64	71.61	72.06	82.68	85.48	73.24	75.81	82.03	81.47	80.9	83.61
15	69.78	72.54	71.72	78.64	73.01	77.88	75.58	73.81	86.65	88.69	75.58	78.34	85.3	87.53	82.03	86.08
20	70.64	75.22	73.01	80.81	75.58	80.17	86.23	73.95	87.28	90.38	81.28	84.14	86.1	88.55	87.4	88.26
25	70.96	77.49	75.16	84.87	81.28	85.87	90.5	92.82	89.53	92.15	85.9	89.48	89.2	89.16	89.2	90.94
30	83.01	79.72	77.73	89.55	86.33	91.05	92.25	94.91	90.18	93.83	87.5	90.17	91.27	92.42	91.37	93.75
35	81.6	82.51	81.28	94.67	90.31	93.63	94.92	95.5	92.67	96.51	89.1	92.54	93.55	94.55	92.87	95.35
40	94.5	95.84	89.88	95.99	93.53	93.86	95.75	96.12	93.16	96.66	93.53	94.11	94.78	96.34	97.49	98.43
45	95.25	96.69	93.08	96.51	94.12	94.91	95.87	97.56	95.57	97.49	94.73	95.83	96.74	97.27	98.09	98.92
50	96.92	97.82	94.92	97.91	95.98	96.33	96.42	98.44	95.79	98.22	96.9	97.34	96.82	98.13	98.24	97.13
55	97.92	98.13	95.22	98.18	96.64	97.13	96.94	98.94	95.7	96.72	97.75	97.73	96.97	98.68	98.82	95.87
60	98.9	98.83	97.69	98.24	98.32	98.38	97.52	98.2	95.77	97.67	98.24	98.78	97.26	97.98	98.97	96.72

x= Dissolution in gastric medium; y = Dissolution in gastric medium with mango juice.

Table 2: Log Percent Remaining of Sample P01 to P08 Gastric Dissolution Medium and in Presence of Mango juice.

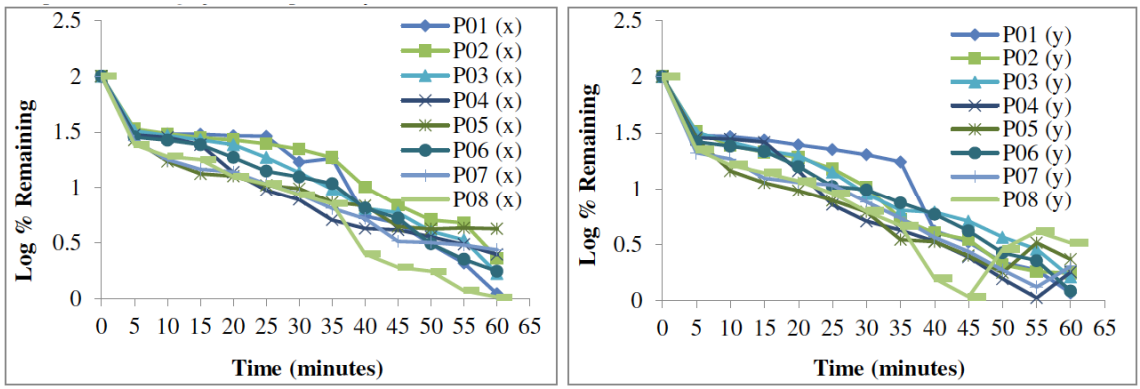
% log Remaining																
Time (min.)	P01 (x)	P01 (y)	P02 (x)	P02 (y)	P03 (x)	P03 (y)	P04 (x)	P04 (y)	P05 (x)	P05 (y)	P06 (x)	P06 (y)	P07 (x)	P07 (y)	P08 (x)	P08 (y)
0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
5	1.50	1.48	1.53	1.51	1.51	1.50	1.48	1.46	1.43	1.44	1.46	1.42	1.42	1.32	1.39	1.35
10	1.48	1.47	1.49	1.39	1.47	1.42	1.45	1.45	1.24	1.16	1.43	1.38	1.25	1.27	1.28	1.21
15	1.48	1.44	1.45	1.33	1.43	1.34	1.39	1.42	1.13	1.05	1.39	1.34	1.17	1.10	1.25	1.14
20	1.47	1.39	1.43	1.28	1.39	1.30	1.14	1.16	1.10	0.98	1.27	1.20	1.14	1.06	1.10	1.07
25	1.46	1.35	1.40	1.18	1.27	1.15	0.98	0.86	1.02	0.89	1.15	1.02	1.03	1.04	1.03	0.96
30	1.23	1.31	1.35	1.02	1.14	0.95	0.89	0.71	0.99	0.79	1.10	0.99	0.94	0.88	0.94	0.80
35	1.26	1.24	1.27	0.73	0.99	0.80	0.71	0.63	0.87	0.54	1.04	0.87	0.81	0.74	0.85	0.67
40	0.74	0.62	1.01	0.60	0.81	0.79	0.63	0.53	0.84	0.52	0.81	0.77	0.72	0.56	0.40	0.20
45	0.68	0.52	0.84	0.54	0.77	0.71	0.62	0.39	0.65	0.40	0.72	0.62	0.51	0.44	0.28	0.03
50	0.49	0.34	0.71	0.32	0.60	0.56	0.55	0.19	0.62	0.25	0.49	0.42	0.50	0.27	0.25	0.46
55	0.32	0.27	0.68	0.26	0.53	0.46	0.49	0.03	0.63	0.52	0.35	0.36	0.48	0.12	0.07	0.62
60	0.04	0.07	0.36	0.25	0.23	0.21	0.39	0.26	0.63	0.37	0.25	0.09	0.44	0.31	0.01	0.52

x= Dissolution in gastric medium; y = Dissolution in gastric medium with mango juice.



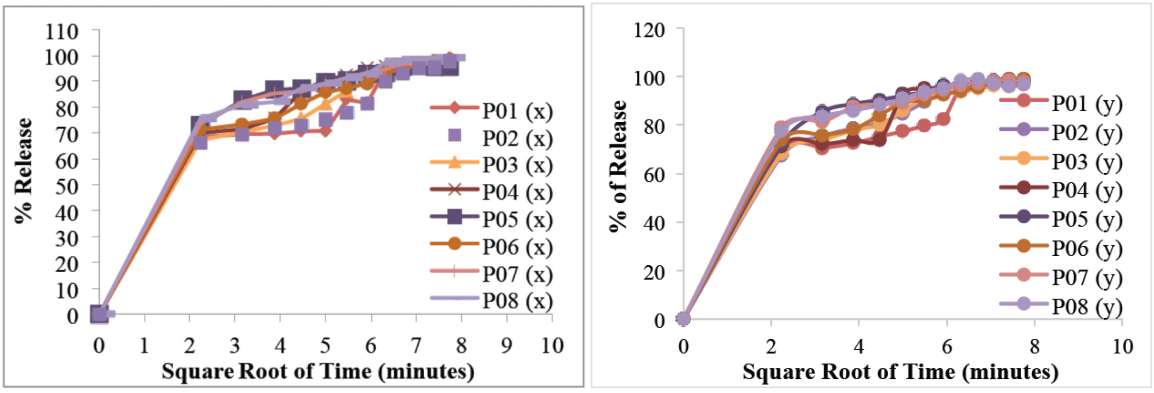
a **b**

Figure 1: Zero Order plots to ascertain release kinetics of different Paracetamol samples (**a**) and Paracetamol samples with mango juice, respectively (**b**).



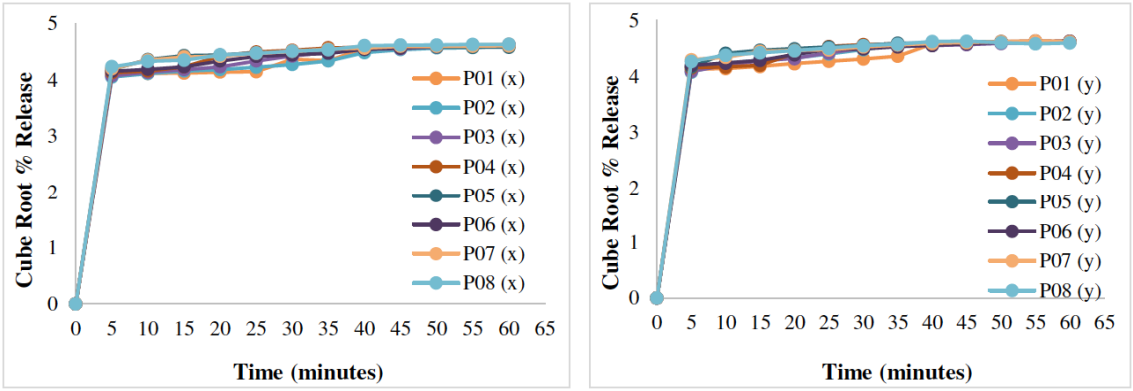
a **b**

Figure 2: First Order plots to ascertain release kinetics of different Paracetamol samples (**a**) and Paracetamol samples with mango juice, respectively (**b**).



a b

Figure 3: Higuchi plots to ascertain release kinetics of different Paracetamol samples (**a**) and Paracetamol samples with mango juice, respectively (**b**).



a b

Figure 4: Hixon-Crowell plots to ascertain release kinetics of different Paracetamol samples (**a**) and Paracetamol samples with mango juice, respectively (**b**).

kinetics models such as Zero Order, First Order, Higuchi, and Hixon-Crowell etc. According to Figures **1-3**. And Figure **4** etc. In this examination, tablets were used as samples, so the initial drug release percentage in 5 minutes of all the drugs, on average, was from 66.23% to 75.58% in dissolution in simulated gastric medium without the mango juice. In presence of mango juice 5 minutes all the drug releases on average 67.42 % to 78.99 % in presence of mango juice on Table **1**. For the logarithm value of the sample percent remaining, Table **2** is depicted. The drug rate of statement was controlled by the increase or decrease in the drug solubility and concentration in the matrix system. Also, dissolution depends on the surrounding medium. In dissolution medium kinetics, Higuchi model was found to be more eminently fitted, which represent percent release vs. square root time (Figure **3**).

Intermediate covering of the mango juice and after 15 to 50 minutes, it was observed that the Paracetamol release increased in the presence of the mango juice. In comparison to the claimed lowest dissolution rate at 10 min, i.e., P02 (70.50%), the highest dissolution rate was of P08 (85.00 %), whereas in the mango juice medium, P02 was 70.62% and P08 was 80.90%.In comparison to the lowest claimed dissolution rate at 20 min, i.e., of P01 (75.63%), the P08 had the highest rate (90.23%), whereas in the mango juice medium, P02 was 75.22 % while P08 was 88.26%.When comparing the lowest claimed dissolution rate at 30 min, P01 was 85.28%, P02 was 89.55 % and P08 was 93.75 %.We can understand that in presence of mango juice, the drug-fruit hindrance was observed, and the height was P08 94.00 % whereas in the mango juice medium, it was when we compared with claimed dissolution of sample drugs. The average results of Paracetamol at 15 to 60 minutes were P01 (98.90%), P02 (97.69%), P04 (95.52%), P06 (98.24%), P07 (97.26%) and P08 (98.97%) remaining in the gastric dissolution medium. Also, in the gastric medium with mango juice, the samples were P01 (98.83%), P02 (98.38%), P04 (98.20%), P06 (98.78%), P07 (97.98 %) and P08 (96.72%).

Which strengths the significance of the reaction between the medication and the mechanisms of mango juice. In digestive dissolution medium without mango juice, Zero Order (Figure **1a**), First Order (Figure **2a**), Higuchi (Figure **3a**) and Hixon-Crowell (Figure **4a**) association coefficient were Zero order 0.45 to 0.65, First Order 0.84 to 0.96, Higuchi 0.68 to 0.83 and Hixson – Crowell 0.28 to 0.36 in the presence of gastric medium. In the digestive dissolution medium without mango juice, Zero Order (Figure **1b**), First Order (Figure **2b**), Higuchi (Figure **3b**) and Hixon-Crowell (Figure **4b**) association coefficient were Zero order 0.41 to 0.62, First Order 0.73 to 0.96, Higuchi 0.68 to 0.83 and Hixson – Crowell 0.28 to 0.36 in the presence of gastric medium with mango juice. Here, we can observe the different correlation coefficient predominant in the dissolution release kinetics. *In vitro* simulated gastric dissolution system with mango juice, Zero Order, First Order, Higuchi and Hixon-Crowell correlation coefficient were demonstrated in Figures **1**, **2**, **3**, and **4** etc. In the above discussion, this study subsequently assumes the faster release rate of 06 brands in overall 08 brands. All the brands were fulfilling according to BP *in vitro* dissolution specification within 45 minutes in acidic media, pharmacopeia requires that the paracetamol tablets should have potency between 95.0 % to 105. 0 %. All products were achieving the requirement in the presence of mango juice. After 1 hour, all brands released higher amount of medicine specifically paracetamol in the presence of mango juice. It is perceived that the mango juice moderately inductees the release of paracetamol *in vitro* dissolution medium. So, we can also apply this method to measure the interference studies of medicine and other common consumable products.

4. CONCLUSIONS

This study is conducted to observe the process which are done by under the representing diverse mathematical models for drug release. To observe the best beneficial properties deprived of any side belongings, the medication must be taken with a glass of pure drinking water and avoid captivating medications with juices and beverages. However, a few of the medication have increased dissolution by beverage and fruit juice. Medicines must not be taken with meal to avoid any food-drug interactions. The physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug. Further study is required to establish the identified results in *in-vivo* models.

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ANNOUNCEMENT OF COMPETING INTEREST

Authors declare that they have no competing interest.

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