Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com

ISSN: 2231-3354
Received on: 30-04-2012
Revised on 04-05-2012
Accepted on: 13-05-2012
DOI: 10.7324/JAPS.2012.2531

A comparative study of the in-vitro dissolution profiles of paracetamol and caffeine combination in different formulations using HPLC

M.E.M. Hassouna, Y.M. Issa and A.G. Zayed

M.E.M. Hassouna
Chemistry Department,
Faculty of Science,
Beni Seuf University,
Beni Seuf, Egypt.

Y.M. Issa
Chemistry Department,
Faculty of Science,
Cairo University, Giza, Egypt.

A.G. Zayed
Head of Quality Control Department,
October Pharma Co., 6th October City,
Egypt.

For Correspondence
M.E.M. Hassouna
Prof. of Analytical chemistry
Chemistry Department,
Faculty of Science, Beni Seuf
University, Beni Seuf, Egypt .
Tel.: +00201223861504

ABSTRACT

Dissolution testing is an in vitro technique of great importance in formulation and development of pharmaceutical dosage forms, as it can be used as a substitute for in vivo studies under strictly defined and specified conditions. The main objective of the present study is to conduct the comparative dissolution studies of various brands of same dosage forms and treatment of obtained dissolution data by using $f2$ to determine whether all the formulations used were equivalent or significantly different. Five different brands of drug containing paracetamol and caffeine from different manufacturers were used in the study, and dissolution testing in different dissolution media viz., water, 0.1 N HCl, phosphate buffer of pH 4.5 and phosphate buffer of pH 6.8 was conducted for 12 tablets from each brand for 60 min. by using dissolution testing apparatus USP type-II. Samples were withdrawn at 10 min. time interval and analyzed for drug content by using HPLC technique. Percent drug release at each time interval was calculated for tablets and the data obtained were treated with statistical technique to meet the FDA requirements for obtaining a waiver of bioavailability and bioequivalence studies.

Keywords: acetaminophen (paracetamol); caffeine; comparative studies of in-vitro dissolution; HPLC.

INTRODUCTION

Panadol® Extra is indicated for the temporary relief of pain and discomfort associated with headache, tension headache, migraine headache, osteoarthritis, arthritis, cold and flu symptoms, toothache, dental procedures, muscular aches, sore throat, period pain and reduces fever. After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma levels occur 10 to 60 minutes after administration. Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved in adults within one hour and the plasma half-life is about 3 to 7 hours.

Caffeine is almost completely metabolized in the liver by oxidation, demethylation and acetylation to various xanthine derivatives, which are excreted in the urine Panadol Extra and Panadol tablets are bioequivalent for $AUC_{0\text{-}10hr}$ and C_{max} for paracetamol. The extent of absorption (AUC) and peak plasma levels (C_{max}) of paracetamol were similar for Panadol® Extra and Panadol tablets. The time to peak plasma level (t_{max}) was not significantly different (http://www.medicines.org.au/files/gcppextr.pdf).

Paracetamol is N-(4-hydroxyphenyl) acetamide, with empirical formula $C_8H_9NO_2$ and has a molecular weight of 151.2 (Eur. Ph., 2008a). Caffeine is 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; with the empirical formula $C_8H_{10}N_4O_2$, and molecular weight of 194.2 (Eur. Ph., 2008b).

Dissolution testing has become an essential tool in the pharmaceutical industry at various stages of development, manufacturing and marketing. For the comparison of dissolution profiles, similarity factor $f2$ is gaining popularity due to its recommendation by various regulatory committees. Dissolution profiles are considered similar if the calculated $f2$ value is between 50 and 100, this acceptance limit might not be correctly defined.

EXPERIMENTAL

Materials and reagents

All materials used in these investigations were of the highest purity available. They included standard grade paracetamol (PA) (Covidien/mallinchrodt Co. LTD USA) and caffeine (CA) (Sinochem, China), with purity of 99.60 and 99.20%, respectively. All these active ingredients were approved in-house working standard in October Pharma Co., 6th October City, Egypt.

Methanol for isocratic chromatography, was obtained from Scharlua, Spain and ultrapure water was prepared using Direct Q Millipore and used to prepare the eluent and to dissolve standards. Tetrabutylammonium hydrogensulphate HPLC grade was obtained from Fluka Chemicals, Switzerland, potassium dihydrogenphosphate, glacial acetic acid and hydrochloric acid (37%v/v) purchased from Scharlua, Spain were of analytical grade and used as received. All other solvents and reagents were of analytical grade or equivalent. Five solid tablets dosage formulations of drug were studied: Panadol® Extra (Batch No.100805, Mfg. date 01/2010, Exp. Date. 12/2013, GlaxoSmithkline, Dungavan Ltd. Ireland) as "innovator" versus Panadol®* Extra tablets "Local manufactruing" (Batch No.100283, Mfg. date 03/2010, Exp. Date. 2/2014, GlaxoSmithkline, Dungavan Ltd. Ireland, under licence: GlaxoSmithkline Consumer Healthcare Ltd. Ireland, Alexanderia Co. For Pharmaceutcials), Abimol® Extra tablets (Batch No. 104010A Mfg. date 12/2010, Exp. Date. 12/2013, GlaxoSmithkline S.A.E, El Salam city, Cairo, Egypt), ProntoPlus® tablets (Batch No.0090111, October Pharma Co., 6th October City, Egypt), Pyril® Extra tablets (Batch No. 01369, Mfg. date 7/2010, Exp. date 7/2013, Kahira Pharm. & Chem. Ind. Co., Cairo, Egypt). They were obtained directly from the manufacturers. The twelve tablets of each brand were individually weighed before use in the dissolution studies, general information of these drugs are reported in table 1.

Dissolution Media

The four dissolution media employed were water, 0.1 N hydrochloric acid, phosphate buffer pH 4.5 and phosphate buffer pH 6.8. The preparations of 0.1 N hydrochloric acid, and phosphate buffer pH 6.8 were from USP (U.S.P, 2011a), while phosphate buffer pH 4.5 was prepared according to European pharmacopoeia (Eur. Ph., 2008c). These media were selected based on the FDA Guidance for Industry and the need to meet the criteria for biowaiver (FDA guidelines, 2000).

Instruments and apparatus

Dissolution apparatus Model Sotax (Switzerland) type AT7 Code (CH-4008) and Varian dissolution apparatus Model VK7000 meet all the USP pharmacopeia requirements (type II paddle), Tablets Hardness tester (Pharma test Tablet testing system Model BT311E), pH meter WTW Inolab (Germany) instrument Model (D82362). Pharma test disintegration tester Model PTZ auto -2, HPLC Agilent model 1200 series, with auto sampler.

Table. 1: General informations.

#	Item	Reference product	Test product			
1	Product name	Panadol® Extra	Pyril® Extra	Panadol®* Extra	ProntoPlus®	Abimol® Extra
2	API (s)	Paracetamol and caffeine				
3	Dosage form	tablets				
4	Route of administration	Oral				
5	Strength (mg)	PA 500, CA 65	PA 500, CA 65	PA 500 ,CA 65	PA 400, CA50	PA 500, CA 30
6	Product description	Oblong tablets	Oblong tablets	Oblong tablets	Round tablets	Oblong tablets
7	Batch number	No.100805	01369	100283	0090111	104010A
8	Mfg. date	01/2010	07/2010	03/2010	01/2011	12/2010
9	Exp. Date	12/2013	07/2013	02/2014	01/2014	12/2013
10	Storage conditions	Below 25°C	Below 30°C	Below 25°C	Below 30°C	Below 30°C

Panadol®* Extra - (Local manufacturing).

Hardness

Hardness was investigated by the "Resistance to crushing of tablets test" according to the. Eur. Ph. (Eur. Ph. 2008d) on a Tablets Hardness tester (Pharma test Tablet testing system Model BT311E)

Uniformity of Mass

Uniformity of Mass was investigated" according to the Eur. Ph. (Eur. Ph. 2008d) on an analytical balance (Sartorius analytical balance)

Disintegration

Disintegration test was investigated" according to the USP Ph. (USP Ph., 2011b) on a disintegration tester (model Pharma test disintegration tester Model PTZ auto -2)

Dissolution Method

Dissolution was carried out using Varian dissolution apparatus Model VK7000 and dissolution apparatus Sotax Model AT7 (Switzerland) digital tablet dissolution test apparatus II, with eight vessels of 1L capacity.

Dissolution of tablets was carried out in 12 vessels, each containing 900 mL of the dissolution media, at 100 rpm. The dissolution media were heated to 37±0.5°C. Three milliliter (3mL) samples were withdrawn at 10, 20, 30, 40, 50, and 60 minutes, and 3 mL of the media was replaced after each withdrawal. The concentration and quantity of the active pharmaceutical ingredients of each sample were determined using liquid chromatography (LC).

LC System

The HPLC system (Agilent model 1200, Germany) consists of separation module with solvent degasser, temperature controlled sample compartment and column heater, and a photodiode array detector. The UV detection was carried out at 210 nm. and a system control was used (Chemistation software) comprising data acquisition, and data processing system to calculate statistical analysis (Microsoft Excel 2007 professional Edition).

Chromatographic Conditions

LC separation was carried out using a HYPERSIL BDS C18 column (150 x 4.6 mm, and 5 µm particle size). All chromatographic experiments were performed in the isocratic mode. The used mobile phase consists of 0.02 mole L^{-1} tetrabutylammonium hydrogensulphate and methanol (100:45, v/v). The flow rate was set at 2 mL min^{-1} and the column was thermostated at 40°C with injection volume of 20 µL.

Standard solutions preparation

27.5 mg of PA was transferred to 50 mL volumetric flask; the PA standard was dissolved in about 40 mL of each of the four dissolution media separately. A 5 mL aliquot of CA stock standard solution containing 72.4 µg mL^{-1} was added to the PA volumetric flask, the volume was completed to the mark with each of the different dissolution media separately, and the finial concentration of PA and CA were 560.00 and 72.40 µg mL^{-1} respectively.

System suitability

A system suitability test was an integral part of the development method to verify that the system is adequate for determination of the mentioned active ingredients. The suitability of the chromatographic system was demonstrated by comparing the obtained parameter values with the acceptance criteria of the ICH guideline (ICH guideline, 1995).

A system suitability test of the chromatography system was performed before each validation run. Six replicate injections of a system suitability/calibration standard and one injection of a check standard were made. Figure 1 shows a typical chromatogram for PA, CA., peak area, retention time (Rt), tailing factor, asymmetry factor, and theoretical plates for the six suitability injections are reported in table 2.

Table. 2: System suitability parameters of the chromatography system .

APIs	Resolution factor (R)	Tailing factor (T)	Peak symmetry (S)	Plate count (TP)	Selectivity (V)	RSD % (Rt)
PA	2.03	1.059	0.92	1969	1.261	0.112
CA	2.09	1.047	0.944	1966	1.246	0.107

Data Analysis

The chemistation software was used to program the HPLC and to acquire and process the primary data. Microsoft Excel 2007 professional Edition was used to calculate the percent dissolved of the active pharmaceutical ingredients (APIs) for 12 individual tablets, and the mean and standard deviation were obtained. The similarity factor, $f2$, was used to compare the dissolution profiles of the different products as required (FDA guideline, 1997).

The difference factor ($f1$) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{\left[\sum_{t=1} n\,|R_t - T_t|\right] / \left[\sum_{t=1} nRt\right]\right\} \cdot 100$$

$$f_2 = 50 \cdot log\left\{\left[1 + (1/n)\sum_{t=1} n\,(R_t - T_t)^2\right] \cdot 0.5 \cdot 100\right\}$$

where n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products (FDA guideline, 1997).

RESULTS AND DISCUSSION

Evaluation of the physicochemical and pharmaceutical properties of tablets showed that all brands fulfilled the requirements of the USP and Eur. Ph. (Eur. Ph. 2008d, USP, 2011b), while each brand showed a significant difference in average weight, dimensions, hardness and disintegration time which corresponded to different mechanism of tablet processing, Table 3 shows physical and pharmaceutical properties of one brand and 4 generic tablets. ProntoPlus® and Pandol* Extra have similarity in matching with Panadol® Extra in average weight and disintegration time; also hardness test that give indication to the similarity in dissolution rate, where disintegration and hardness are effective factors in the dissolution rate. The dissolution rate of the active ingredient from a formulation is mainly related to the surface characteristics of the tablet. In contrast, the release rate of the active ingredient of Pyril® Extra is lower than that observed for Panadol® Extra and ProntoPlus® in all the studied media, according to dissolution profile data.

Table 3. Physical parameters.

	Weight (mg)	Thickness (mm)	Length (mm)	Hardness (Kp)	Disintegration time (min)
Panadol® Extra					
n*	**20**	**10**	**10**	**10**	**12**
Mean	695.06	6.29	18.20	15.75	8.94
Min.	699.30	6.46	18.29	17.30	10.18
Max	689.90	5.88	17.91	13.50	8.10
SD	2.57	0.23	0.14	1.28	0.87
RSD%	0.37	3.70	0.77	8.15	9.71
Pyril® Extra					
Mean	1008.20	6.56	21.29	20.38	21.29
Min.	1022.10	6.96	21.69	24.30	22.19
Max	975.50	6.27	21.08	17.40	19.17
SD	12.60	0.28	0.26	2.33	1.01
RSD%	1.25	4.33	1.22	11.41	4.76
Panadol*® Extra					
Mean	689.28	6.29	18.11	15.14	9.19
Min.	701.30	6.50	18.35	17.30	10.15
Max	673.40	5.83	17.70	12.80	8.10
SD	9.00	0.28	0.27	1.61	0.87
RSD%	1.31	4.43	1.49	10.63	9.41
ProntoPlus®					
Mean	596.17	3.95	13.12	18.37	8.82
Min.	598.50	3.97	13.15	19.80	10.10
Max	592.90	3.91	13.10	17.30	8.36
SD	1.50	0.02	0.01	0.66	0.58
RSD%	0.25	0.47	0.10	3.59	6.54
Abimol® Extra					
Mean	607.24	5.88	16.69	13.39	18.97
Min.	626.90	5.92	17.15	15.40	21.01
Max	596.50	5.83	16.58	9.20	17.22
SD	9.06	0.03	0.17	1.76	1.02
RSD%	1.49	0.52	1.03	13.13	5.40

n* Number of tested tablets

Water is often used as the dissolution medium, but is not always suitable for several reasons: the quality of water can varies depending on the source of water, the surface tension may be variable and depends on the types of excipients present in the formulation and the pH value is inherently difficult to measure because it can vary from day to day and may also change during the run depending on the active substance and excipients (U.S. Pharmacopeial Forum, 2004). Tables 4-7 as a calculation examples show the dissolution profile results in water, 0.1 mol L^{-1} HCl and phosphate buffers pH 4.5 and 6.8 at each interval for comparison between Panadol® Extra as an innovator and 4 local drugs. A product is said to be rapidly dissolving when not less than 85% of the labeled API dissolves within 30 minutes (FDA guidelines, 2000). As evidenced from results reported in tables, the products tested can be said to be rapidly dissolving in the four media, The dissolution rate of all drugs released between 80 and 100% within 30 min. and showed faster releases in acidic medium than those obtained both at pH 4.5 and 6.8, Figs. 2 and 3 show the high similarity between Panadol® Extra and Panadol®* Extra during all intervals in the four dissolution media; the products tested can be said to have the same ingredients, processing and physical parameters, that prove that the local manufacturing of Panadol®* Extra has the highest quality, compared with the Panadol® Extra. The similarity of the dissolution profiles was determined using the similarity factor, $f2$ (FDA guidelines, 1997). Two dissolution profiles are considered to be similar when the $f2$ value is greater than 50 and dissimilar when less than 50 (FDA guidelines, 2000). The $f2$ was not determined for the comparison of products with more than 85% release of AIP in 15 min because they were established to be very rapidly dissolving. The only circumstance in which $f2$ is not required according to the Guidance (FDA guidelines, 1997), is when 85% or more of the labeled amount of the drug dissolves in fifteen minutes. The $f2$ values were calculated only up to the first point at which 85% release was achieved and at the 30-min time point. Subsequently, $f2$ and $f1$ factors were calculated to determine the similarity of Panadol®* Extra with Panadol® Extra in the four dissolution media; the reported data are considered as good evidence that Pandol* Extra is similar to innovator (Panadol® Extra). The calculations of $f2$ are not less than 50 and the difference factor $f1$ are form 1 to 4 for PA and CA active ingredients. Using the same rules, the results in case of ProntoPlus® versus Panadol® Extra, prove that ProntoPlus® have the same dissolution rate in comparative dissolution versus Panadol® Extra although Panadol® Extra has different strengths of PA and CA than Panadol® Extra. Data recorded in tables showed that $f2$ values in case of the four used media were not less than 50 and those for $f1$ were not more than 15, so that ProntoPlus® drug is considered an approved drug, Figs 2 and 3 show the comparative dissolution curves in case of Panadol® *Extra and ProntoPlus® versus Panadol® Extra as innovator. The different conclusions of similarity for Pyril® Extra and Abimol® Extra versus Panadol® Extra in the four dissolution media were obtained by applying the calculation of $f1$ and $f2$ factors. As shown in tables 6 and 7, the values of $f2$ and $f1$ were out of limits ($f2 < 50$ and $f1 > 15$), in the four dissolution media. For CA and PA, the dissolution occurred with different rates and the dissolution profiles for Pyril® Extra and Abimol® Extra versus Panadol® Extra (innovator) were dissimilar although Pyril® Extra has the same strengths of both PA and CA as Panadol® Extra, however the similar strengths are considered as ineffective factors in comparative dissolution. Fig. 4 shows the comparative dissolution profiles of Panadol® Extra (innovator) reference versus Pyril® Extra test in phosphate buffer pH 6.8 as an example figure.

Table. 4: Dissolution profiles of Panadol® Extra against ProntoPlus® using water as a dissolution medium.

Dissolution Profiles of PA						ƒ1, ƒ2 statistical analysis			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	86.15	79.88	83.17	10 min.	83.17	100.93	17.76	315.35
	Tt	103.47	98.72	100.93	20 min.	88.31	101.24	12.93	167.16
20 min.	Rt	90.59	85.49	88.31	30 min.	92.44	102.03	9.59	91.95
	Tt	103.59	98.90	101.24	40 min.	92.61	101.65	9.04	81.72
30 min.	Rt	93.10	91.33	92.44	50 min.	93.44	102.69	9.25	85.52
	Tt	103.22	99.99	102.03	60 min.	94.27	103.73	9.46	89.41
40 min.	Rt	93.17	91.93	92.61					
	Tt	102.38	101.24	101.65		sum (Rt-Tt)			68.02
50 min.	Rt	94.01	92.76	93.44		sum (Rt-Tt)2			831.11
	Tt	103.42	102.29	102.69		sumRt			544.25
60 min.	Rt	94.84	93.59	94.27		**Similarity factor *f*2**			**46**
	Tt	104.46	103.33	103.73		**Difference factor *f*1**			**12**
Dissolution Profiles of CA						**ƒ1, ƒ2 statistical analysis**			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	95.13	91.01	92.12	10 min.	92.12	100.76	8.65	74.74
	Tt	104.95	98.25	100.76	20 min.	97.83	98.67	0.84	0.70
20 min.	Rt	100.82	95.30	97.83	30 min.	102.56	99.94	2.63	6.91
	Tt	100.58	94.05	98.67	40 min.	102.43	99.02	3.41	11.65
30 min.	Rt	103.64	100.10	102.56	50 min.	104.58	101.82	2.77	7.66
	Tt	102.71	96.21	99.94	60 min.	106.74	104.62	2.12	4.50
40 min.	Rt	104.50	99.85	102.43					
	Tt	100.86	94.64	99.02		sum (Rt-Tt)			20.41
50 min.	Rt	106.66	102.00	104.58		sum (Rt-Tt)2			106.16
	Tt	103.66	97.44	101.82		sumRt			606.27
60 min.	Rt	108.81	104.16	106.74		**Similarity factor *f*2**			**69**
	Tt	106.46	100.24	104.62		**Difference factor *f*1**			**3**

Table. 5: Dissolution profiles of Panadol® Extra against ProntoPlus® using 0.1N HCl as a dissolution medium.

Dissolution Profiles of PA						ƒ1, ƒ2 statistical analysis			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	88.20	82.85	85.01	10 min.	85.01	98.67	13.65	186.42
	Tt	99.73	97.23	98.67	20 min.	90.94	100.46	9.52	90.66
20 min.	Rt	93.05	89.46	90.94	30 min.	93.22	100.77	7.55	57.06
	Tt	101.10	99.15	100.46	40 min.	91.03	99.28	8.25	68.03
30 min.	Rt	94.01	92.50	93.22	50 min.	93.53	100.51	6.98	48.77
	Tt	101.94	99.72	100.77	60 min.	94.37	101.56	7.19	51.74
40 min.	Rt	92.36	89.02	91.03					
	Tt	100.41	98.44	99.28	sum (Rt-Tt)				53.15
50 min.	Rt	94.51	92.12	93.53	sum (Rt-Tt)2				502.69
	Tt	101.26	99.34	100.51	sumRt				548.10
60 min.	Rt	95.35	92.95	94.37		**Similarity factor *f*2**			**52**
	Tt	102.30	100.39	101.56		**Difference factor *f*1**			**10**
Dissolution Profiles of CA						**ƒ1, ƒ2 statistical analysis**			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	100.74	95.36	97.33	10 min.	97.33	102.75	5.42	29.34
	Tt	139.80	98.23	102.75	20 min.	103.45	101.61	1.84	3.38
20 min.	Rt	105.94	98.66	103.45	30 min.	105.64	102.82	2.81	7.90
	Tt	103.90	99.42	101.61	40 min.	101.07	100.15	0.92	0.85
30 min.	Rt	109.32	103.32	105.64	50 min.	105.34	102.30	3.05	9.28
	Tt	105.48	101.21	102.82	60 min.	107.47	105.06	2.41	5.80
40 min.	Rt	102.47	99.45	101.07					
	Tt	103.07	97.34	100.15		sum (Rt-Tt)			16.44
50 min.	Rt	110.18	102.64	105.34		sum (Rt-Tt)2			56.54
	Tt	104.01	101.52	102.30		sumRt			620.30
60 min.	Rt	112.30	104.77	107.47		**Similarity factor *f*2**			**75**
	Tt	106.78	104.29	105.06		**Difference factor *f*1**			**3**

Table. 6: Dissolution profiles of Panadol® Extra against Pyril® Extra using Phosphate buffer pH 4.5 as a dissolution medium.

Dissolution Profiles of PA						ƒ1, ƒ2 statistical analysis			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	58.53	57.63	58.00	10 min.	58.00	49.95	8.06	64.88
	Tt	50.33	49.41	49.95	20 min.	76.48	84.69	8.21	67.45
20 min.	Rt	77.50	75.45	76.48	30 min.	78.44	94.78	16.35	267.17
	Tt	87.34	81.46	84.69	40 min.	80.21	97.06	16.85	283.98
30 min.	Rt	80.03	77.14	78.44	50 min.	80.24	98.27	18.03	324.88
	Tt	96.75	92.90	94.78	60 min.	80.97	99.55	18.58	345.31
40 min.	Rt	80.78	79.58	80.21					
	Tt	100.49	94.22	97.06		sum (Rt-Tt)			86.0716
50 min.	Rt	80.73	79.46	80.24		sum (Rt-Tt)2			1353.67
	Tt	99.43	96.88	98.27		sumRt			454.30
60 min.	Rt	81.46	80.19	80.97		**Similarity factor *f*2**			**41**
	Tt	101.83	96.75	99.55		**Difference factor *f*1**			**19**

Dissolution Profiles of CA						ƒ1, ƒ2 statistical analysis			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	69.66	67.05	67.71	10 min.	67.71	37.56	30.15	908.90
	Tt	42.34	34.23	37.56	20 min.	90.10	82.71	7.39	54.62
20 min.	Rt	92.37	87.89	90.10	30 min.	90.19	95.33	5.14	26.43
	Tt	84.62	78.84	82.71	40 min.	92.21	97.44	5.23	27.30
30 min.	Rt	92.79	87.13	90.19	50 min.	92.16	97.90	5.74	32.95
	Tt	96.74	93.17	95.33	60 min.	94.16	98.80	4.64	21.55
40 min.	Rt	94.20	90.32	92.21					
	Tt	102.39	93.45	97.44		sum (Rt-Tt)			58.29
50 min.	Rt	94.15	90.30	92.16		sum (Rt-Tt)2			1071.75
	Tt	100.00	95.68	97.90		sumRt			526.53
60 min.	Rt	96.14	92.29	94.16		**Similarity factor *ƒ*2**			**44**
	Tt	102.37	94.96	98.80		**Difference factor *ƒ*1**			**10**

Table. 7: Dissolution profiles of Panadol® Extra against Pyril® Extra using Phosphate buffer pH 6.8 as a dissolution medium.

Dissolution Profiles of PA						ƒ1, ƒ2 statistical analysis			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	66.46	64.68	65.95	10 min.	65.95	50.72	15.22	231.76
	Tt	55.87	46.79	50.72	20 min.	76.69	79.27	2.57	6.62
20 min.	Rt	77.34	76.17	76.69	30 min.	76.84	90.82	13.99	195.39
	Tt	82.44	75.68	79.27	40 min.	78.21	93.61	15.41	237.32
30 min.	Rt	77.49	76.46	76.84	50 min.	77.46	94.14	16.68	278.04
	Tt	92.66	86.07	90.82	60 min.	78.29	94.58	16.29	265.29
40 min.	Rt	78.41	77.96	78.21					
	Tt	97.51	92.61	93.61		sum (Rt-Tt)			80.14
50 min.	Rt	78.27	76.97	77.46		sum (Rt-Tt)2			1214.42
	Tt	98.65	92.90	94.14		sumRt			453.43
60 min.	Rt	79.10	77.79	78.29		**Similarity factor *ƒ*2**			**45**
	Tt	98.79	92.95	94.58		**Difference factor *ƒ*1**			**14**
Dissolution Profiles of CA						**ƒ1, ƒ2 statistical analysis**			
Interval		Max%	Min%	Mean%	Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10 min.	Rt	76.44	75.69	76.19	10 min.	76.19	44.69	31.50	992.24
	Tt	51.91	40.99	44.69	20 min.	96.48	79.34	17.14	293.90
20 min.	Rt	98.78	92.57	96.48	30 min.	94.85	94.44	0.41	0.17
	Tt	83.72	75.19	79.34	40 min.	97.72	98.45	0.73	0.53
30 min.	Rt	97.74	92.82	94.85	50 min.	92.16	98.25	6.09	37.11
	Tt	99.20	88.14	94.44	60 min.	94.25	98.51	4.26	18.17
40 min.	Rt	100.00	93.37	97.72					
	Tt	105.12	96.46	98.45		sum (Rt-Tt)			60.14
50 min.	Rt	95.14	91.06	92.16		sum (Rt-Tt)2			1342.12
	Tt	105.45	95.33	98.25		sumRt			551.65
60 min.	Rt	97.23	93.16	94.25		**Similarity factor *ƒ*2**			**41**
	Tt	104.20	95.73	98.51		**Difference factor *ƒ*1**			**11**

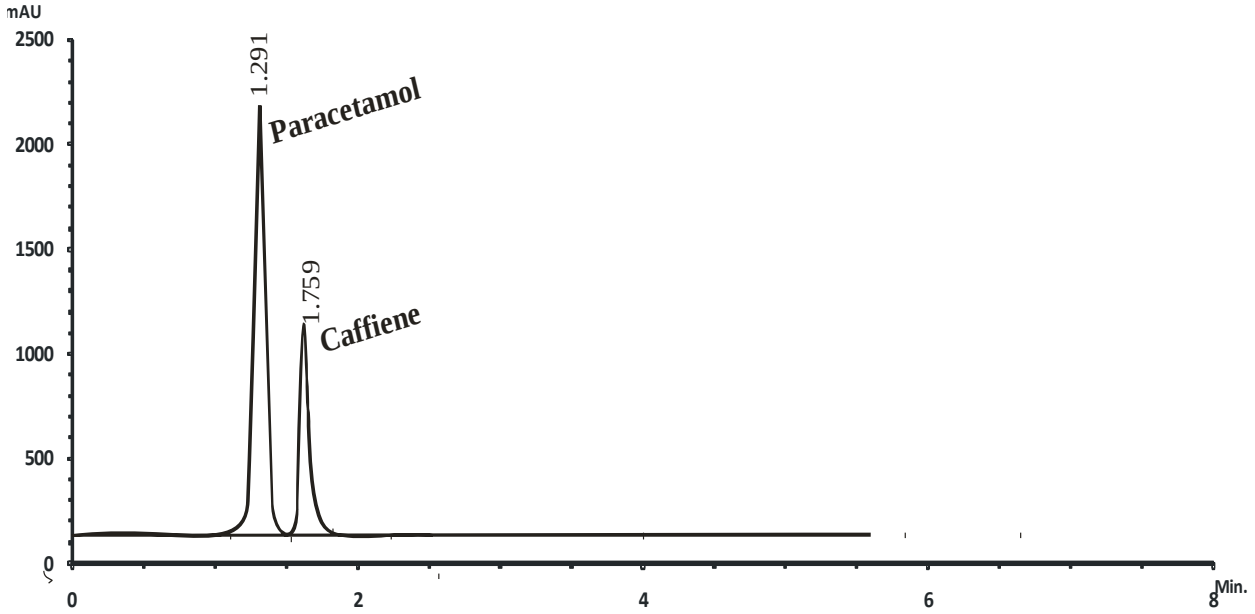

Fig. 1: A typical chromatogram for PA and CA.

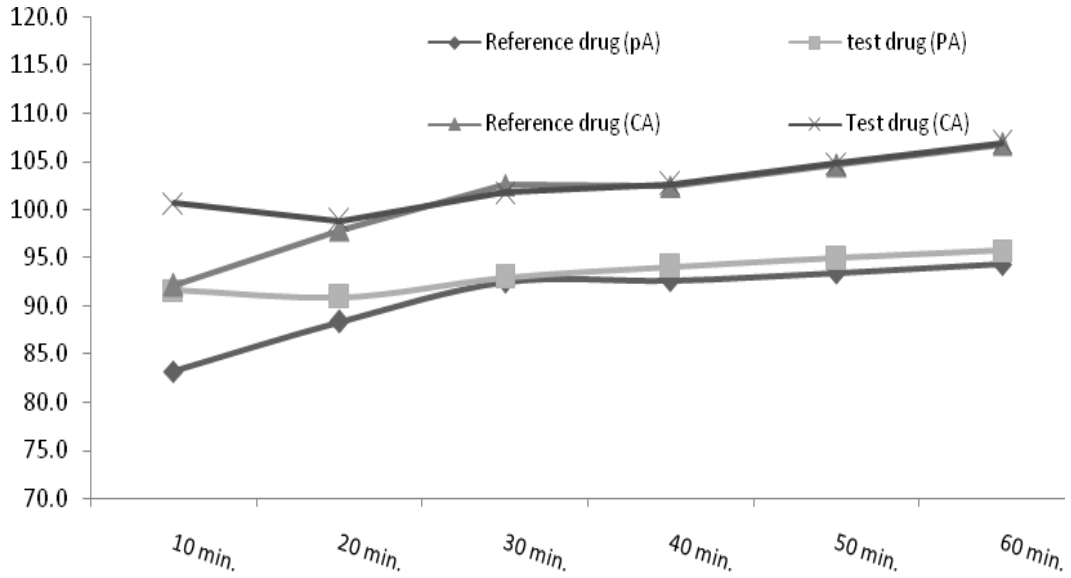

Fig. 2: Comparative Dissolution Profiles Of Panadol ® Extra (Innovator) Reference Versns Panadal ® *Tested In Water.

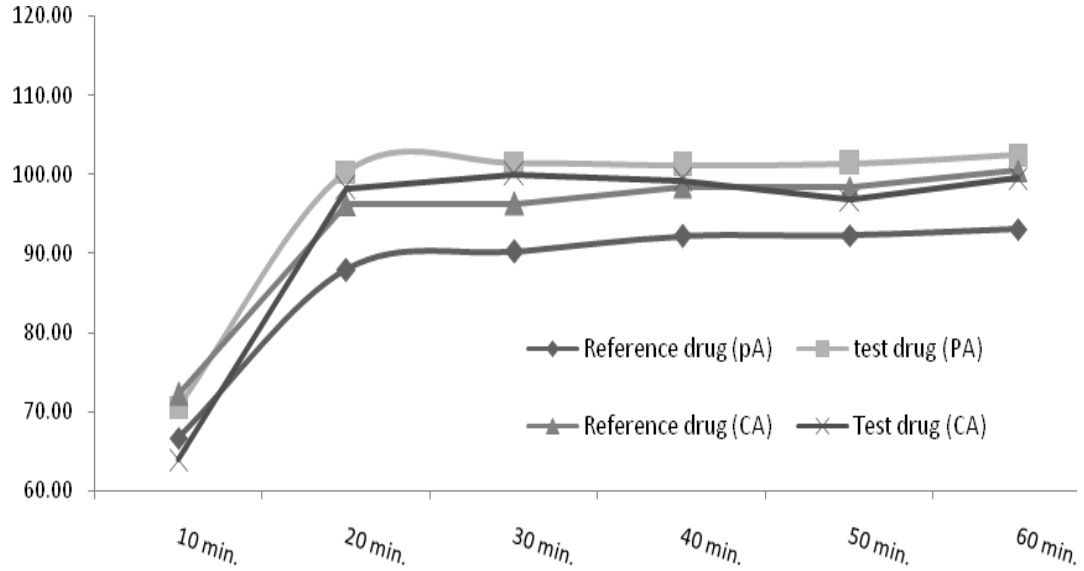

Fig. 3: comparative dissolution profiles of Panadol ®Extra (innovator) reference versus Prontoplus ®tested in phosphate buffer pH 4.5

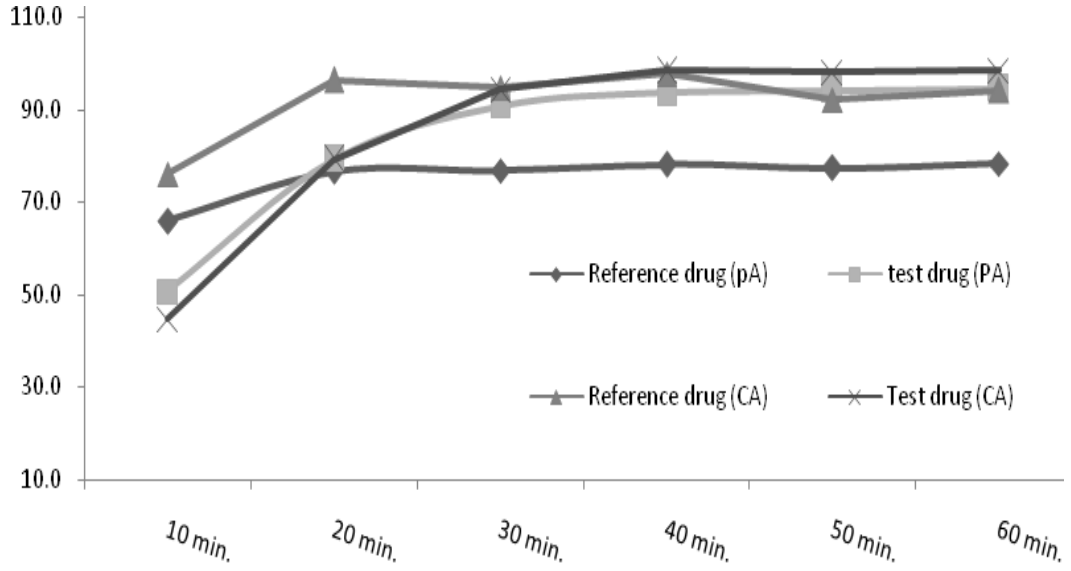

Fig. 4: comparative dissolution profiles of Panadol® Extra (innovator) referece vetsus Pyril® Extra test in phosphate buffer pH 6.8

Table. 8: Summary of similarity factors *f*2 and difference factors *f*1 for studied drug brands in different media.

Medium	**Water**		**0.1 N HCl**		**Phosphate Buffer pH 4.5**		**Phosphate Buffer pH 6.8**	
Active ingredients	*PA*	*CA*	*PA*	*CA*	*PA*	*CA*	*PA*	*CA*
Product Name								
Panadol®* Extra								
f2	71	72	97	73	54		68	58
f1	3	2	2	2	5	7	2	4
ProntoPlus®								
f2		69	52	75	51	70	51	55
f1	12	3	10	3	10	3	7	7
Pyril® Extra								
f2								
f1		13				10	14	11
Abimol® Extra								
f2	51					52	51	
f1	10	11			13	8	10	

00 Factors out of limit (f2 less than 50, f1 more than 15)
00 Factors in the allowable range (f2 more than 50, f1 less than 15)

CONCLUSIONS

The differences in release characteristics among multi-sourced PA and CA tablets suggest likely implications for the bioavailability of the active ingredient, thus questioning the interchangeability of the products. Nevertheless, further advice would be needed to determine whether the observed in vitro differences are of any clinical significance. So that the in-vitro comparative dissolution was considered as indicating studies for determination the comparative dissolution between multi-sourced drugs with different formulations and strengths versus the reference drugs, and can be used as a substitute for in vivo studies under strictly defined and specified conditions. Our suggested study discusses the comparative dissolutions for multi-sourced PA and CA drugs with the reference ones. The study reached to the conclusion that Pandol* Extra (Locally manufactured) and ProntoPlus® drugs are similar to the reference drug (innovator) while Pyril® Extra and Abimol® Extra are dissimilar to the reference drug, due to Pyril® Extra and Abimol® Extra have different formulations and physical characteristics. This doesn't mean that Pyril® Extra and Abimol® Extra are not effective, but they must be subjected to in-vivo clinical study to give full reports. Table 8 shows summary of the obtained data to clarify the similarity *f*2 and difference *f*1 factors in all cases.

REFERENCES

Dissolution Testing of Immediate Release Solid Oral Dosage Forms; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, (1997).

European pharmacopoeia 6th Edition, Vol. II, Paracetamol, Ph Eur Monograph 0049, the quality of medicine & Healthcare of the council of Europe (EDQM), (2008a): 1364.

European pharmacopoeia 6th Edition, Vol. II, Paracetamol, Ph Eur Monograph 0267, the quality of medicine & Healthcare of the council of Europe (EDQM), (2008b): 2611.

European pharmacopoeia 6th Edition, Vol. I, Buffer solution chapter, Ph Eur Monograph 4.1.3 the quality of medicine & Healthcare of the council of Europe (EDQM), (2008c): 509.

European pharmacopoeia 6th Edition, Vol. I, method of analysis chapter, Ph Eur Monograph2.9.5, 2.9.8 the quality of medicine & Healthcare of the council of Europe (EDQM), (2008d): 278, 279.

ICH, Topic Q2A-Note for Guidance on Validation of Analytical Methods: Definitions and Terminology (CPMP/ICH/381/95) and Topic Q2B- Note for Guidance on Validation of Analytical Procedures: Methodology (CPMP/ICH/281/95), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1995).

U.S. Pharmacopeia national formulary, thirty four editions, vol. I, Buffer solution chapter, (2011a): 964, 965

U.S. Pharmacopeia national formulary, thirty four edition, vol. I, Disintegration chapter<701>, (2011b): 276

U.S. Pharmacopeial Forum. 1092. The Dissolution Procedure: Development and Validation, vol. 30, No. 1, The United States Pharmacopeial Convention, Inc., Rockville, MD, (2004): 351–364.

Waiver of In Vivo Bioavailability and Bioequivalence studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration,Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office:Washington, DC, (2000).