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COMPARATIVE QUALITY ASSESSMENT OF ACETAMINOPHEN IMMEDIATE AND EXTENDED RELEASE TABLETS BY VALIDATED ANALYTICAL METHODS

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Abstract: In this study quality performance of four immediate release and three extended release acetaminophen tablets were evaluated by using *in vitro* dissolution and drug content studies. Other general quality parameters of these tablets like weight variation, hardness, friability, disintegration time were also determined according to established protocols. UV spectroscopic and RP-HPLC methods were validated and used to determine the active ingredients in these brands. All the brands complied with the official specification for friability, uniformity of weight, disintegration time and drug content. The results were also subjected to statistical analysis. Potency obtained from UV method and HPLC methods were found similar with statistical t test. Dissolution test results were subjected to further analysis by difference factor (f1), similarity factor (f2), dissolution efficiency (% DE), ANOVA and Bonferroni test. The results indicated that all the immediate release brands are similar in respect of drug release. On the other hand and 2 out of 3 extended release brands are found similar.

Keywords: Acetaminophen, Immediate release tablet, Extended release tablet, Dissolution comparison.

INTRODUCTION

A product must possess some criteria to claim it to be a quality product. Organoleptic properties (size, shape, DT, thickness, hardness and friability), Potency and dissolution are the main criteria used to assess quality of a product. Organoleptic properties are the physical criteria of a dosage form which are essential for physical stability and patient's acceptability of the product. Potency is the amount of drug present in the product and accurate potency is essential for optimum plasma drug label and subsequent pharmacological actions. The therapeutic efficacy of a drug product intended to be administered by the oral route depends on its rate and extent of absorption by the gastrointestinal tract. After administration tablet breaks down into granules and small fragments that facilitate dissolution and plays a vital role in liberation a drug from its dosage form and making it available for subsequent gastrointestinal absorption. So, dissolution analysis of pharmaceutical solid dosage forms is also a very important test of product quality [1].

Acetaminophen is one of the most popular over-the-counter drugs. It has analgesic and antipyretic properties with weak anti-inflammatory activity and it is used in the symptomatic management of moderate pain and fever [2]. When taken at recommended doses it has an excellent safety profile [3]. It is available in different dosage forms: tablet, capsules, drops, elixirs, suspensions and suppositories [4]. The drug is official in different pharmacopeia [5-6]. USP contains monograph of both immediate and extended release acetaminophen tablet. Immediate release tablets provide a specific drug concentration in systemic circulation without offering any control over drug delivery but extended release (ER) tablet formulations maintain uniform drug levels, reduce dose and side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance. Both immediate release and extended release acetaminophen tablets are available in the market.

Quality assessment of locally available acetaminophen immediate release tablet has been reported earlier [7]. But no such information is available on recently launched acetaminophen extended release tablets. On the other hand most of

researchers used less sensitive UV Spectroscopic methods for drug analysis. Thus an initiative was taken to check the current status of acetaminophen immediate release and extended release tablets by a validated UV Spectroscopic as well as RP-HPLC method.

Selective and sensitive analytical method for quantitative determination of drugs and their metabolites are essential for successful evaluation of clinical pharmacology, pharmacokinetics (PK), bioavailability (BA) and bioequivalence (BE) studies. Acetaminophen is official in BP and USP. Analysis methods are described in these pharmacopeias. UV[8] and HPLC[9] methods for the analysis of acetaminophen are also reported in the literature. Most of the methods are applicable for multi-component dosage form and they are not free from limitations. But it this study we have validated both UV spectroscopic and RP-HPLC method and used them acetaminophen analysis and compare these two methods by paired *t* Test, so that one can test acetaminophen tablet with their available facility.

The proposed methods were validated for the parameters like linearity, accuracy, precision and robustness as per ICH guidelines [10]. The linearity of an analytical method is its ability to elicit that test results are proportional to the concentration of drug in samples within a given range. Linearity of the method is generally determined by constructing calibration curves. The accuracy is the closeness of agreement between the true value and test result. Accuracy is determined by means of recovery experiments. The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple samplings of the same homogeneous sample under prescribed conditions. It is determined by calculating % RSD of various measurements at different time, lab, equipment or analyst.

MATERIALS & METHOD

Reagents and Materials

Acetaminophen was provided by Aristo Pharma Limited, Dhaka, Bangladesh. Methanol was of HPLC grade and was purchased from E. Merck, Darmstadt, Germany. Other reagents were of analytical-reagent grade and purchased from E. Merck, India. Water was deionised and double distilled. Marketed formulation of acetaminophen tablet 500 mg (Four brands denoted as IR-1, IR-2, IR-3 and IR-4) and acetaminophen extended release tablet 650

mg (Three brands denoted as ER-A, ER-B, ER-C) were purchased from local drug store in Dhaka city after checking their manufacturing license number, batch number, production and expiry date. Validation of UV Spectroscopic Method

A double-beam Shimadzu (Kyoto, Japan) UV-Visible spectrophotometer, Model UV-1700 PC, equipped with 1 cm quartz cells, with a fixed slit width (1 nm), wavelength accuracy of +0.5 nm (with automatic wavelength correction) was used. The drug analyses data were acquired and processed using UV Probe software (Version 2.0, Shimadzu, Japan) running under Windows XP on a Pentium PC. For scanning, the wavelength range selected was from 300 nm to 220 nm with medium scanning speed. (Figure 1)

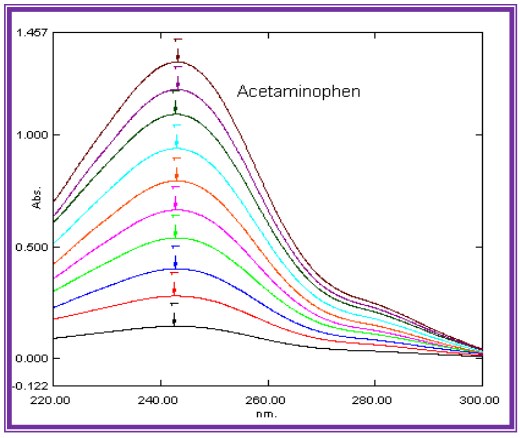

Figure1. Spectrum of acetaminophen (2-20 mcg/ml)

The proposed method was validated for the parameters like Selectivity, linearity, accuracy, precision and robustness as per ICH guidelines [10].

Selectivity of the method was determined by comparing the spectrum of standard acetaminophen with that of market product.

Linearity of the method was determined by constructing calibration curves in pH 5.8 phosphate buffer (dissolution medium for acetaminophen tablet) and in simulated gastric fluid (dissolution medium for acetaminophen extended release tablet). Stock solution of acetaminophen (100mcg/ml) was prepared in both the media and diluted to get standard solution across the range of 2-20 mcg/ml. The measured absorbance for different concentration of acetaminophen were plotted to get calibration curve and linearity was measured by observing correlation coefficient (R^2 value).

Accuracy was determined by means of recovery experiments. Solution of known concentration of acetaminophen was prepared from placebo formulation and absorbance was measured and potency was calculated. The accuracy was assessed from

the test results as the percentage of the drug recovered by the assay.

The precision of the method was investigated with respect to repeatability (inter assay precision), ruggedness (inter day precision) and reproducibility (inter laboratory trial). Repeatability was determined by performing three repeated analysis of the three standard solutions (4, 8, 12 µg/ml) on the same day from 9.00 am to 9.00 pm, under the same experimental conditions. Ruggedness (inter day precision) of the method was assessed by carrying out the analysis of standard solutions on three different days (inter-day) in the same laboratory. For reproducibility the procedure repeated in another lab by using another Shimadzu spectrophotometer (model: UV-1601). The relative standard deviation (% RSD) was calculated in order to assess the precision of the method.

To determine the robustness solvent of different pH was used to dissolve the drug. Percent recovery was calculated to examine the robustness.

Validation of RP-HPLC Method

A Shimadzu (Japan) HPLC system consisting of a CMB-20 Alite system controller, two LC-20AT pumps, SIL-20A auto-sampler and CTO-10ASVP column oven were used. Ultraviolet detection was achieved at 243 nm with a SPD-20A UV-VIS detector (Shimadzu, Japan). The drug analyses data were acquired and processed using LC solution (Version 1.3, Shimadzu, Japan) software running under Windows XP on a Pentium PC. The mobile phase, water: methanol (60:40 v/v), was pumped at a flow rate of 1.0 ml/min through the column (C_{18}; 250 mm X 4.6 mm, 5µ shim-pack, Japan) at ambient temperature. The mobile phase was filtered through a 0.2µ nylon membrane filter and degassed prior to use under vacuum. Elusions were analyzed by UV detector at a sensitivity of 0.0001.

Stock solution of acetaminophen (100mcg/ml) was prepared in the mobile phase and diluted to get standard solution 80%-120% of target concentration. The method was validated for the parameters like system suitability, selectivity, linearity, accuracy, precision and robustness

The system suitability was assessed by six replicate analyses of standard solution at a 100% level to verify the resolution and reproducibility of the chromatographic system. This method was evaluated by analyzing the repeatability of retention time,

tailing factor, theoretical plates (Tangent) of the column.

To determine the selectivity of the method standard samples of acetaminophen and commercial immediate release and extended release formulations were injected in the system. The chromatograms were analyzed for retention time, peak area and peak shape to determine selectivity of the method.

Linearity was determined by means of calibration graph that was constructed with increasing amount of standard solutions (80%, 90%, 100%, 110% and 120% of target concentration). These standards were tested six times in agreement to the International Conference on Harmonization (ICH). The proposed method was evaluated by correlation coefficient of calibration graph.

Accuracy and precision were determined by performing four repeated analysis of the three standard solutions (90%, 100% and 110% of target concentration) on three different days. % Recovery was calculated to access accuracy and % RSD was calculated to access precision.

The robustness of the method was assessed by altering the some experimental conditions such as by changing the flow rate from 0.9 to1.1 ml/min and amount of methanol (38% to 42%) in the mobile phase.

Evaluation of acetaminophen tablets

Various physico-chemical parameters of these tablets like weight variation, hardness, friability, disintegration time were determined according to established protocols.

Determination of uniformity of weight

20 tablets from each of the 5 brands were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, JAPAN). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Hardness test

Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

Friability test

20 tablets of each brand were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India) at 25 rev/min for 4 min. The tablets were then weighed and

compared with their initial weights and percentage friability was obtained.

Disintegration test

6 tablets from each brand were employed for the test in distilled water at 37°C using Tablet Disintegration Tester (Model: VDT-2, Veego, India). The disintegration time was recorded as the time required to pass the tablet completely through the sieve and no particle remained on the basket of the system.

Determination of potency of acetaminophen tablets

20 Tablets were weighed and finely powdered. Powder containing about 50 mg acetaminophen was dispersed in 100 ml phosphate buffer (pH 5.8), shaken for 10 min and sonicated for 5 min and diluted upto 250 ml. 10.0 mL of this solution was again diluted with *phosphate buffer* to 200 ml, filtered and used for absorbance measurement in a double-beam Shimadzu (Kyoto, Japan) UV-Visible spectrophotometer (Model UV-1700 PC) to find out the potency. The samples were also prepared in mobile phase in the same way and injected in Shimadzu (Japan) HPLC system. Potency was calculated from peak area.

Dissolution test

The dissolution test was done using tablet dissolution tester (TDT-08L, Electrolab, India) in 5 replicates for each brand. Phosphate buffer (pH 5.8) and simulated gastric fluid were used as dissolution media for acetaminophen tablet and acetaminophen extended release tablet respectively. The medium was maintained at 37 ± 0.5°C. In all the experiments, 10 ml of dissolution sample were withdrawn at predetermine time interval and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by validated UV Spectroscopic method. The concentration of each sample was determined from a calibration curve obtained from pure samples of acetaminophen.

Data analysis

The uniformity of weight was analyzed with simple statistics while the dissolution profiles were analyzed by difference factor (f1), similarity factor (f2), dissolution efficiency (% DE) ANOVA and Bonferroni test. Potency measured by two different methods was compared by paired *t* Test.

RESULTS AND DISCUSSION

Validation of UV Spectroscopic method

UV spectroscopic method for acetaminophen analysis was found selective

as spectrum of standard acetaminophen coincide with that of market product indicating that excipients has no noticeable effect on the effectiveness of the method.

The proposed method was found to be linear in the concentration range (2-14 mcg/ml). Correlation coefficient was 0.999 in both the dissolution media which proves the high linearity of the method. (Figure 2)

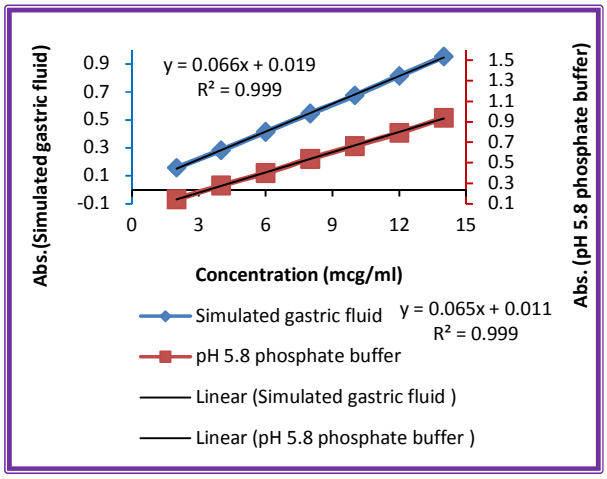

Figure 2 Calibration curve of acetaminophen in simulated gastric fluid (◊) and pH 5.8 phosphate buffer ( )

Results of accuracy, precision (repeatability, ruggedness, reproducibility) and robustness are summarized in table 1. The method was found accurate as indicated by results of recovery studies (%recovery was 99.7%-100.14%), highly precise (% RSD is less than 2%) and robust as no significant effect was observed in the recovery of drugs dissolved in different media.

Validation of HPLC Method

The experiment was carried out according to the official specifications of USP, ICH-1995, and Global Quality Guidelines.

Table 2 represents system suitability test results of this method. The system is found suitable in respect of retention time (% RSD 0.236) mean theoretical plate count (more than 5000), tailing factor (less than 1.5).

Acetaminophen Peaks of standard solution and sample of immediate release tablets and extended release formulations were on same time (Figure 3). Excipients did not change the retention time or interfere the analysis results. So the method is highly selective for acetaminophen.

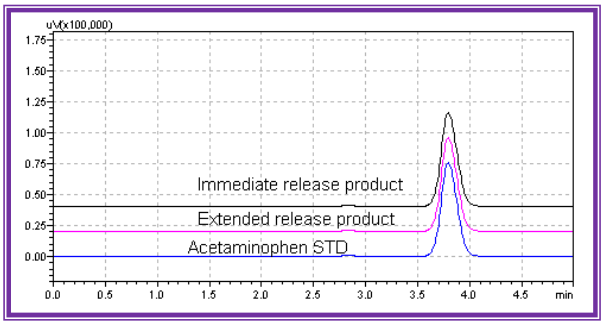

Figure 3 Chromatogram of acetaminophen and marketed brands

Results of linearity, accuracy and precision were summarized in table 3. The method was found linear as regression co efficient of calibration curve is more than 0.999. Average % recovery was 100.04 ± 0.37 and %RSD in precision was 0.35-0.924. So the method is highly accurate and precise.

* R^2 = regression coefficient

**Y = mX+C; where Y = peak area, m = slope, X = concentration (mcg/ml) and C = intercept.

Robustness study was performed by making a slight variation in flow rate and amount of methanol in mobile phase. No significant effect was observed in the recovery of drugs. % recovery was 98% to 102%. On the other hand changes in retention time, theoretical plate and resolution were also negligible. So we can say that the method is robust.

Properties of tablets

All the brands had low tablet weight variation (SD < 3.5). Crushing strength of the tablets was in the range of 56 to 226 N and percentage weight loss in the friability test was ≤ 0.5% in all the brands. Disintegration time (DT) of the tablets in all the brands showed 78.37-129.00 sec. Overall, the tablets were of good quality with regard to crushing strength, friability, weight uniformity and disintegration time (table 4).

Potency of tablets

The validated UV spectroscopic and HPLC methods were used to determine the potency of commercially available immediate and extended release acetaminophen tablets (table 5). Potency was found 97%-104.37%. Potency calculated from UV method and HPLC method was compared by paired *t* Test at 0.05 significance level. The P-value was greater than the delineated significance level, indicating that there was no statistically significant difference between the two methods.

***In vitro* drug release study**

The release profiles of different immediate release brand (IR-1 to IR-4) and extended release brands (ER-A, ER-B and ER-C) of acetaminophen tablets are shown in Figs 4 and 5. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results.

USP specification for acetaminophen immediate tablet is that not less than 80% (Q) of the labeled amount of acetaminophen ($C_8H_9NO_2$) should dissolve in 30 minutes. All the brand complied with the USP specification. Around 80% drug was released within 10 min and around 100%

drug was released within 30 min from all the immediate release brands.

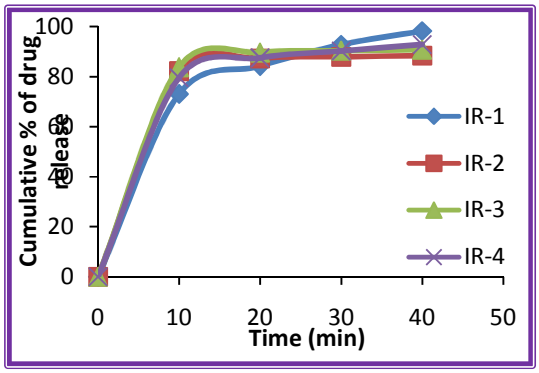

Figure 4. Drug release from different immediate release acetaminophen formulations (IR-1 to IR-4)

USP describes multi point dissolution test method for extended release acetaminophen tablet. USP specification for drug release from acetaminophen extended release tablets is 45-65% in 15 min, 60-80% in 1 hour and not less than 80% in 3 hour. The dissolution profile of three extened release acetaminophen tablets was found different. ER-A complied the USP specification at the lower limit site. On the other hand ER-C complied with the USP specification at the higher limit site. But brand ER-B did not comply the release limit at 15 min and 1 hour time point. It complied with release limit of 3 hr time point.

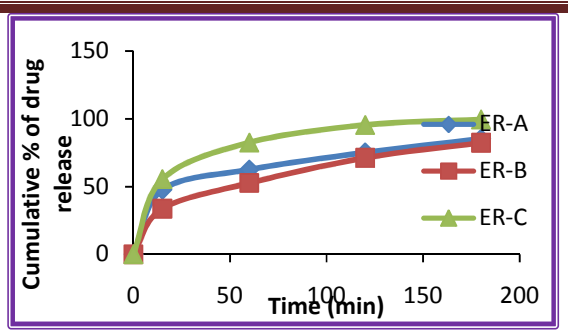

Figure 5. Drug release from different extended release acetaminophen formulations (ER-A to ER-C)

Comparison of dissolution data

Difference factor (f1), similarity factor (f2) and dissolution efficiency (%DE) were calculated to compare the dissolution profile. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) 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. The following equations were used to calculate difference factor f1 and similarity factor f2.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log\left\{\left(1+\frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right)^{-0.5} X100\right\}$$

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

Similarity factor f2 has been adopted by FDA (1997) and the European Agency for the Evaluation of Medicinal Products (EMEA, 2001) by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile [11-12]. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100.

Dissolution efficiency (DE) was also employed to compare the drug release from various brands. Dissolution efficiency is the area under the dissolution curve within a time range (t1 - t2). DE was calculated by using the following equation:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_i - t_{i-1})(y_{i-1} + y_i)}{2}$$

Where *y* is the percentage dissolved at time *t*

Table 6 shows the f1, f2 and % DE of immediate release and extended release tablets of acetaminophen. Brand IR-1and ER-C were used as reference product to calculate f1 and f2.All the immediate release brands are similar with reference brand IR-1 as in all the cases f2 were greater than 50 and f1 were less than 15. But extended release brands, ER-A and ER-B were not similar with the reference brand ER-C.

Table 6 also shows the dissolution efficiency of different brands. Higher dissolution efficiency was found in case of brand IR-3 (immediate release brand) and ER-C (extended release brand). The reference brand and the test products can be said to be equivalent if the difference between their dissolution efficiencies is within appropriate limits (± 10%, which is often used) [13]. All immediate release brands are equivalent to reference brand as difference of % DF (test product – reference product) is less than 10. However, extended release brands are not similar with reference brand.

The percentage dissolved was also tested statistically to ascertain differences among brands using one-way analysis of variance (ANOVA) while Bonferroni test was employed to find out the homologous groups. The analyses were undertaken for time points 30 min (for immediate release brands) and 180 min (for extended release brands). These time points were chosen

because 80% drug should be released from immediate release tablets within 30 min as per USP official dissolution specification. On the other hand 180 min is the last time point of multipoint dissolution test for extended release acetaminophen tablets according to USP.

The results of ANOVA as shown in Table 7 and 8 indicated that the percent dissolved was similar in case of immediate release products but significantly different in case of extended release products at 0.05 significance level.

According to Multiple Comparisons Bonferroni test homologous brand are shown in table 9. Immediate releases brands are homologous to each other but only ER-A and ER-B of extended release brands were found homologous to each other.

CONCLUSION

The present study was undertaken with an aim to evaluate the immediate release and extended release acetaminophen tablets. The study indicates that only the immediate release tablets are similar with each other but extended release brands are not similar with each other. Furthermore one of the extended release brand did not comply with the compendia specification of drug release. Although the study was performed on limited in vitro experiments, yet on the basis of professional judgment the data reported in this paper clearly indicate that constant surveillance on the marketed drugs by the government, manufactures and independent research groups is essential to ensure availability of quality medicines.

ACKNOWLEDGMENT

The authors are thankful to Aristo Pharma Ltd for providing paracetamol as gift samples.

Table 1

Data showing accuracy, precision and robustness of UV spectroscopic method

Validation parameters		Concentration (mcg/ml)		
		4	8	12
Accuracy	% Recovery ± SD	100.14 ± 0.27	100.11± 1.03	99.7± 0.42
Precision (%RSD)	Repeatability	0.37	0.27	0.095
	Ruggedness	0.52	0.43	0.25
	Reproducibility Lab-I	1.38	0.84	0.87
	Reproducibility Lab-II	1.62	0.96	0.93
Robustness % Recovery ± SD	Phosphate Buffer pH 5.8	100.04 ± 0.37	100.01± 1.30	99.75± 0.59
	Phosphate Buffer pH 6.8	100.04 ± 0.37	100.11± 1.02	99.57± 0.72

Table2

Results of system suitability study

Parameters	Average	SD	%RSD
Retention time	3.782	0.001	0.236
Area	225268.800	3218.493	1.429
Theoretical plates	5872.333	3.391	0.058
Tailing factor	1.127	0.003	0.288

Table 3

Linearity, accuracy and precision results of HPLC method

Validation parameters		Acetaminophen
Linearity (regression coefficient-R^2) (*Y = mX+C)	R^2 (mean±SD)	0.9993±0.0004
	%RSD **	0.04
	Slope (mean±SD)	1548.16±32.72
Accuracy	% Recovery	99.74 ± 0.41
Precision (%RSD)	%RSD	0.41
	Repeatability	0.56
	Ruggedness	0.93
	Reproducibility	1.47

Table 4

Physical properties of the acetaminophen formulations

Formulations	Thickness (mm) ± SD (n = 5)	Hardness (N) ± SD (n = 6)	Friability (%) (n = 20)	Weight (mg) ± SD (n = 20)	DT (Sec ± SD)
IR-1	6.77 ± 0.05	56 ± 6.56	0.27%	618.24 ± 3.12	129.00 ± 0.89
IR-2	4.85 ± 0.08	103 ± 8.73	0.25%	629.44 ± 2.73	78.37 ± 0.19
IR-3	4.95 ± 0.05	226 ± 8.93	0.15%	587.18 ± 2.13	91.80 ± 0.42
IR-4	4.46 ± 0.06	191 ± 7.62	0.19%	624.83 ± 3.18	100.5 ± 0.71
ER-A	6.15 ± 0.09	115 ± 3.38	0.10%	720.66 ± 1.23	
ER-B	5.96 ± 0.10	203 ± 6.82	0.12%	723.66 ± 3.11	
ER-C	7.13 ± 0.04	204 ± 7.56	0.17%	1022.14 ± 2.18	

Table 5

Potency of the acetaminophen formulations

Brands	UV method		HPLC method		t-value	p
	Absorbance	Potency	Peak Area	Potency		
IR-1	0.539	99.81	150,179	100.00	1.06	0.329
IR-2	0.542	100.37	156,747	104.37		
IR-3	0.537	99.44	151,648	100.98		
IR-4	0.545	100.93	145,671	97.00		
ER-A	0.535	99.07	156,325	104.09		
ER-B	0.532	98.52	151,079	100.60		
ER-C	0.542	100.37	149,988	99.87		

Table 6

f1, f2 and % DE of acetaminophen tablets

Brand	f2	f1	%DE
IR-1			87.5864734
IR-2	56.70800359	7.68200572	86.8347826
IR-3	57.15754593	7.42995941	89.084058
IR-4	65.9842203	5.0608904	87.9903382
ER-A	38.35897188	19.3946926	69.3512611
ER-B	30.6704155	28.6125212	62.260352
ER-C			85.7353883

Table 7

Results of analysis of variance at 30 min time point for immediate release tablets

	Sum of Squares	DF	Mean Square	F	Sig.
Between Groups	21.400	3	7.133	1.594	.230
Within Groups	71.600	16	4.475		
Total	93.000	19			

Table 8

Results of analysis of variance at 180 min time point for extended release tablets

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	819.433	2	409.717	69.248	.000
Within Groups	71.000	12	5.917		
Total	890.433	14			

Table 9.

Homogeneous group of acetaminophen tablets

Brands	Homogeneous group
IR-1	IR-2, IR-3, IR-4
IR-2	IR-1, IR-3, IR-4
IR-3	IR-1,IR-2, IR-4
IR-4	IR-1,IR-2, IR-3
ER-A	ER-B
ER-B	ER-A
ER-C	

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