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TWIN BATCH ANALYSIS PROTOCOL TO FACILITATE THE ANALYSIS OF HIGH-THROUGHPUT PHARMACEUTICAL PRODUCTS

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ABSTRACT

Purpose: The study proposes a model 'Twin Batch Analysis Protocol' for the speedy determination of product quality. The quality of two batches of paracetamol tablets combined in a 1: 1 proportion was determined considering it as a single batch. The analytical work load in high throughput products could be reduced by almost 50%. **Methods:** The analytical data of past records from a pool of 80 batches extending over an eight-year period were compared with actually generated analytical data of 40 batches to determine the consistency of product quality. Under twin batch analysis, data generated from individual analysis of two tablet batches were compared with the results of twin batch analysis data of the same two batches combined together in a 1:1 proportion. **Results:** Deviation of results between the two batches involved in conventional single batch analysis and twin batch analysis in all parameters (not applicable to dissolution) were less than 3%. Successful determination of assay values of blinded samples prepared with different strengths of paracetamol confirmed the integrity of the analyst. **Conclusion:** The procedure set out here could be considered as a useful model "Twin Batch Analysis Protocol' that could be adopted by the pharmaceutical industry. It suits products that are manufactured in a large number of batches reducing the analytical work load by 50%.

KEYWORDS: Paracetamol tablets, product dossier, subdivision of tablets, twin batch analysis, therapeutic ratio.

INTRODUCTION

The objective of any pharmaceutical manufacturing organization is to manufacture products of necessary attributes speedily, at low cost and with minimal environmental pollution. This project was undertaken to design an analytical protocol termed 'Twin Batch Analysis Protocol' (TBAP) that would save resources almost by 50% for selected dosage forms. Given the current difficulties in economics, resourcing, and logistics the advantage of the protocol is very relevant. The TBAP document is intended to be considered as an integral part of the product dossier.[1]

Instead of conventional testing of single batches, the quality of two batches is tested simultaneously in the proposed method. Strict criteria were laid down to be satisfied by a given product to qualify for twin batch analysis. The protocol is proposed on the basis of extensive investigations undertaken here and the directive under General Notices in the British Pharmacopoeia that facilitates the industry to adopt analytical methods other than what is specified.[2] The responsibility in adopting the procedure and its outcome lies with the manufacturer according to the principle adopted by the European Pharmacopoeia which does not provide monographs for most of the dosage forms. There are multinational pharmaceutical companies that analyse one in five batches of high throughput products and release all five batches on the basis of their stringent quality assurance measures.

Environmental pollution in the pharmaceutical industry can be reduced with the twin batch analysis.[3] The procedure can reduce the workload of repeated analysis in selected products that are being regularly produced in large quantities. When a product is made well within prescribed specifications repeatedly over and over again

for a prolonged period of time, it is natural that an idea comes to scale down the analytical work load. TBAP facilitates paying greater attention on the rest of the analytical work related to other products as well as work related to Quality Assurance.[4,5]

Product criteria qualifying candidature for TBAP

Product criteria that qualify candidature in the selection for twin batch analysis are as follows.

i) Assessment of the past manufacture of a 'defect free' finished product in all applicable specifications consistently over a prolonged period, 8 years in this case.[6, 7]
ii) The product should have a high concentration of a single active ingredient, over 80% w/w in the case of paracetamol tablets assessed here.
iii) Candidate dosage form should have limited scope for content variation.
iv) The active ingredient should have a wide 'therapeutic ratio'.[8, 9]
v) Products should be in high demand with large number of batches being produced routinely over a prolonged period.
vi) The protocol is valid for immediate release solid dosages without any rate measurements. Gastro-resistant preparations could also be considered.
vii) Exclusion criteria include life-saving, critical care or emergency drugs. Drug products with a history of quality detected by the manufacturer or reported by an official analytical laboratory disqualifies candidature for TBAP.

The protocol should be considered as an integral part of the product dossier kept in readiness for inspection by the regulatory authorities. These criteria will effectively eliminate all products with inconsistencies in quality and discourage a glut of candidate drugs to be subjected to Twin Batch Analysis Protocol.

Paracetamol (Acetaminophen) tablets manufactured by the State Pharmaceuticals Manufacturing Corporation (SPMC), Ratmalana, Sri Lanka, were selected as the prospective candidate product for twin batch analysis. This was established by deciphering the details of manufacturing and quality control records from a pool of 80 batches at the Quality Control Department of SPMC. According to SPMC, on the average two paracetamol tablet batches of 448 kg, each equivalent to 0.8 million tablets were being manufactured daily. Each tablet weighs 560 mg and contains 500 mg of paracetamol.

A large amount of data practically generated during the study, together with past reports confirm the uniformity of product characteristics within a given batch and between the batches. On this account, the product meets the United States Food and Drug Administration definition of a batch with regard to homogeneousness.[10]

Studies have found that paracetamol may enter the environment mainly from manufacturing sites and as laboratory waste. The huge operational cost associated with the procedures which remove those chemicals from the environment has made them an undesirable choice.[11] Hence twin batch analysis should be a welcome option for obtaining pharmaceutical products with considerably reduced cost and minimal environmental pollution. All these criteria taken together are expected to constitute the requirements for a sound TBAP. Product quality validation can also be considered as one of the most important parts of Quality Assurance.[12] The study indicated that none of the analytical parameters showed any significant difference between the single batch and twin batch analysis. Almost all values fall within less than 3% difference between them.

METHODS

The 'current' samples or batches refer to tablet batches being freshly manufactured within one and a half months from the date of manufacture during the study period. 'Shelf' samples or batches mean the batches that had been already manufactured prior to the study period, nearing the end of shelf life period and are falling within the last three months of their expiry period. These two extremes of the shelf- life period of the batches was selected for the twin batch analysis protocol. The experiments were carried out in the Quality Control Department of SPMC and the Pharmaceutical Analytical Laboratory, Department of Chemistry, University of Colombo, Sri Lanka.

The following instruments were used for the analysis. Electronic scale: METTLER AE, 027038, 1986, Japan. UV-Visible spectrophotometer: AGILENT TECHNOLOGIES, Japan and Laminar flow cabinet: model BIOBASE. Tableting machine: HATA IRON WORKS, 38 station, model HT-AP38MS-U, Japan. Sodium hydroxide pellets: MERCK SPECIALTIES Pvt Ltd and potassium dihydrogen orthophosphate: FISHER SCIENTIFIC UK Ltd were used as chemical reagents.

Establishing paracetamol tablets as a candidate product for twin batch analysis protocol

The product quality evaluation process consisted of two steps.

Step One: Carrying out data analysis of past records of batches already made and marketed. This included 20 older batch manufacturing records and analytical reports covering the period 2009 - 2011 and another more recent 60 reports covering the period 2011-2017. Taken together the 80 batches cover over 8 years period of manufacture. Data analysis on individual batches were undertaken to confirm whether past quality standards were within the specification and to confirm that the paracetamol tablets deserve to be subjected to TBAP.

Step Two: Based on data analysis under step one confirming acceptability of quality, actual laboratory analysis of randomly selected batches of tablets were under taken. As a part of a rigorous validation process, analysis of batches representing two extremes of the

shelf- life period was carried out. These included, (a) tablets of 20 fresh batches 'currently' being processed during the study period and (b) 'Shelf' samples of 20 batches falling within the last 3 months of the three years shelf- life period. The results were tabulated on the basis of the above three categories, Step One, Step two (a) and Step Two (b) (Table 1). Parameters analyzed were weight variation, friability, hardness, assay and dissolution.

Weight variation of half portion of divided tablets from 'current' and 'shelf samples was also determined (Table 2).[13] Viable microbial counts were also determined for the current and shelf samples nearing expiry date in order to determine the microbial quality. Blinded samples diluted with excipient were subjected to assay to confirm that the analyst was not biased.

Twin batch analysis design

Twin batch analysis was carried out based on Paracetamol Tablets B.P. monograph but by combining (twining) two batches in the proportion 1: 1 instead of the usual single batch. In all parameters tested, the results of the two individual constituent batches to be twined were compared with the twin batch analysis results for reproducebility of results. The idea was to find out following twining, whether the results yielded comparable values with those of constituent batches. The dissolution was performed by combining one half portion of each of the divided tablets belonging to two batches that were to be used in the twin analysis. (Figure 1) The additional surface area resulting from division of the tablets was ignored in the study. The assay and dissolution tests were repeated in the Pharmaceutical Analytical Laboratory, Department of Chemistry, University of Colombo as the second laboratory to confirm reproducibility.

Scheme for twin batch analysis for assay

Current samples

Randomly selected batches were paired together from a pool of 20 fresh paracetamol tablet batches currently being manufactured during the study period. A total of 14 such paired samples were analyzed, first the constituent single batches and then as 14 pairs combined in a 1: 1 proportion subjected to the twin batch assays in duplicate adding up to 56 assay determinations (Table 3).

Shelf samples

From a pool of 20 older shelf samples in the last three months of their shelf- life period was subjected to single batch wise analysis and then to the twin batch analysis in duplicate. A total of 10 such paired samples were analyzed totaling 40 assays (Table 4).

Individual assay results of the two paired constituent batches were compared with twin batch assay results.

Three different schemes were followed in combining (twining) the paired batches as explained under legends in tables 3 and 4. This is for the robustness of the analysis giving maximum scope for any possible variations. First method was to take half the number of tablets recommended in the British Pharmacopeia from each of the two constituent batches. Second method was to take one dose unit (a tablet) from each of the two batches and the third was to take half the dose unit (half a tablet) from each of the two batches expecting the last combination to give maximum deviation.

In the second laboratory, assays were performed using a similar set of combination schemes for the current and older shelf samples (Tables 5 and 6) and the results compared.

Blinded excipient diluted tablet analysis

Required number of paracetamol tablets were powdered. Samples with three dilution levels 100%, 50% and 25% w/w of the label claim were prepared by diluting with lactose unknown to the researcher conducting the analysis. These experiments were to check if the expected assay values will be determined following analysis and that the analyst is free of bias. (Table 7).

Twin batch analysis for dissolution

Paracetamol tablet batches were individually subjected to conventional dissolution tests. These batches were then randomly paired for the twin batch dissolution tests. One half of the split tablets from each of the two paired batches were combined and used in the twin batch dissolution tests. (Figure 1). This procedure was adopted since twining is not possible with the use of a single unit dosage used in the conventional dissolution test. Four such twin batch dissolution tests were performed for each of the current and older shelf samples from the paired batches (Table 8). Same procedure was repeated in the second laboratory using two dissolution tests each for current and shelf samples (Table 9).

Twin batch friability and hardness tests

Friability of two individual paracetamol tablet batches from each of the current and shelf samples were determined. Two batches were paired together and ten tablets from each of the paired batches were combined for the twin batch test to represent twenty tablets recommended for the test (Table 10).

Similarly two tablet batches were selected for the hardness test. Five tablets from each batch were paired together, instead of ten tablets from a single batch for the twin batch test. (Table 11).

Microbial viable count test for individual tablet batches (Current and shelf samples)

Soya bean casein digest agar (SCD) plates were prepared under sterile conditions. Five paracetamol tablets were placed in a sterile mortar and they were crushed into a fine powder. Crushed powder (1 g) was placed in a boiling tube and 9 ml of sterilized phosphate buffer solution (pH 6.8) was added. Solution was stirred using a

sterilized glass road and allowed to stand for about 10 minutes. The supernatant of the solution (1 ml) was added to the corner of Petri plate and sterilized media (20 ml) was poured into the other corner of the Perti plates. Plates were kept for a while and were closed and moved clockwise 5 times and counter clockwise 5 times. Plates were sealed and incubated at 32 ^{0}C in an incubator for 24 hours and continued to observe at 25 ^{0}C for a further 48 hours. Two samples each from a single batch of current and shelf samples were tested (Table 12).

RESULTS

The data analysis of 80 randomly selected past batch records for seven parameters spanning a period of eight years showed that paracetamol tablets had been manufactured to meet all required specifications and therefore the study could be undertaken. The data generated by actual laboratory analysis for 40 batches confirmed that the tablets meet all the specifications (Table 1). These 120 analyses laid a data bank for the undertaking of the TBAP.

The weight variation results of half tablet portions too met the specifications (Table 2).

All the assay values in the twin batch analysis tabulation for the 'current' batches lie well within the 95 – 105% of label claim, minimum being 97.16% and maximum 102.93% (Table 3). A maximum deviation of 1.54% was found between average assay values in columns A and B for single batch analysis and twin batch analysis. There is a general trend of greater degree of deviation from five tablet combination to half tablet combination as given in the table legend.

The parallel study of 'shelf' samples yielded assay results almost identical to the current samples. A maximum deviation of 1.95% was found between columns A and B (Table 4). It is less than 3% between individual batches in columns a. or b. and B in both tables 3 and 4. Here again, a greater deviation was noted when tablet halves are subjected to twin batch analysis. These results show that for a rigorous validation process, use of half or single tablets for twin batch analysis should be preferred if that is analytically feasible for the product concerned.

The second laboratory assay test results of both current and shelf samples for single batch and twin batch analysis reflect similar values to that of first laboratory (Tables 5 and 6). Comparing fresh batches with those of older shelf batches nearing end of shelf life has shown that the analytical results are very similar even at the extremes of shelf- life period. Blinded analysis too is encouraging since only a maximum of -0.38% difference from the expected values was seen for the three samples analyzed (Table7).

In the twin batch dissolution tests with combined tablet halves, all the values are close to or more than 100%. These results hold good for the second laboratory as well. The results on this important dissolution parameter are exceptionally good (Tables 8 and 9). Twin batch analysis results are marginally higher than single batch analysis possibly due to larger surface area from the newly exposed surfaces following splitting the tablets in to two. Tables 8 and 9 shows that the dissolution values of two tablet halfs are approxymately 3% higher than those of single tablets. Current samples and shelf samples from two extremes of shelf- life period also do not show any significant differences.

The comparative analytical results for friability and hardness are given in Tables 10 and 11. All the friability values are well within the limit of 1.0%.

Microbiological colony count test results on current and shelf samples are given in Table 12. The microbial counts were determined only for a single batch each for both current and shelf samples. The colony counts for all determinations for bacteria and fungi are 0 – 20, well within the compendia limits of 100 colonies for bacteria and for fungi.

Table I: Summary of data analyzed and regenerated laboratory analyzed data for quality evaluation of randomly selected paracetamol tablet batches.

Test	Data analysis of past batch analytical records (N = 80)		Batches subjected to laboratory analysis		Specification
			Current batches (N=20)	Shelf samples (N = 20)	
Weight variation (Target tablet weight = 560 mg)	Min	550.9	557.1	556.0	(± 5%) of average tablet weight
	Max	580.6	563.7	563.1	
Friability %	Min	0.05	0.06	0.10	Not more than 1%
	Max	0.88	0.37	0.41	
Hardness (Kilopascal)	Min	5.7	9.5	7.1	(8 – 16 In house)
	Max	14.0	11.8	10.2	
Disintegration test (min)	Min	0.6	0.8	0.7	Not more than 15 min
	Max	7.5	1.4	2.0	
Assay (%)	Min	95.78	97.19	97.20	95-105 % of label claim
	Max	102.40	102.28	100.88	
Dissolution (%)	Min	80.69	95.16	87.10	Not less than 80 % in 30 min
	Max	107.87	104.72	107.87	

Table II: Single batch weight variation test results of tablet halves.

Sample	Minimum weight of half a tablet (mg)	Maximum weight of half a tablet (mg)	Average Weight (mg)	Range (±5% of 280 mg)
Current Sample (N= 20)	274	288	282	268 - 296
Shelf Sample (N= 20)	279	306	293	278 - 308

Table III: Comparative single and twin batch assay results of paractamol tablets (Current Samples).

No	Assay % of two batches used for twin analysis		Average assay (A) = (a+b)/2	Twin batch duplicate assay % using same batches (a) and (b) combined.			Deviation (A-B)
	Batch 1 (a)	Batch 2 (b)		Sample1 (c)	Sample2 (d)	Average assay (B) = (c+d)/2	
01	99.04	100.95	99.99	98.78	98.12	98.45	+1.54%
02	97.46	101.32	99.39	98.02	99.44	98.73	+0.66%
03	97.19	101.01	99.10	97.16	99.89	98.52	+0.58%
04	97.65	99.80	98.73	98.39	100.44	99.42	-0.70%
05	99.30	98.73	99.02	98.81	98.75	98.78	+0.24%
06	99.93	99.21	99.57	99.73	98.74	99.24	+0.33%
07	99.90	99.05	99.48	100.35	99.57	99.96	-0.48%
08	101.24	99.71	100.48	100.51	100.67	100.59	-0.11%
09	101.53	99.75	100.64	98.28	99.91	99.10	+1.53%
10	102.28	98.74	100.51	100.43	102.93	101.68	-1.16%
11	97.46	101.32	99.39	99.18	98.62	98.90	+0.49%
12	99.30	98.73	99.02	100.03	99.72	99.88	-0.87%
13	99.93	99.21	99.57	98.63	97.72	98.18	+1.40%
14	99.90	99.05	99.48	97.82	98.02	98.01	+1.48%

Method 1 - Combined five tablets from each batch (a) and (b) for twin analysis (c) and (d) under numbers 1 – 8. Method 2 – Similarly combined one tablet from each batch for twin analysis in numbers 9 – 11. Method 3 – Similarly combined half a tablet from each batch for twin analysis in numbers 12-14.

Table IV: Comparative single and twin batch assay results of paracetamol tablets (Shelf samples).

No	Assay % of two batches used for twin analysis		Average assay (A) = (a+b)/2	Twin batch duplicate assay % using same batches (a) and (b) combined			Deviation (A-B)
	Batch1 (a)	Batch 2 (b)		Sample1 (c)	Sample2 (d)	Average assay (B) = (c+d)/2	
01	100.08	97.90	98.99	100.80	100.24	100.52	-1.53%
02	97.88	98.13	98.00	99.17	99.78	99.48	-1.50%
03	100.88	98.49	99.69	99.40	100.52	99.96	-0.27%
04	99.55	98.51	99.03	99.63	99.81	99.72	-0.70%
05	99.89	97.80	98.85	100.12	99.94	100.03	-1.19%
06	98.72	100.56	99.64	99.58	97.71	98.64	+1.00%
07	97.20	99.90	98.55	98.73	98.48	98.61	-0.06%
08	98.50	100.14	99.32	101.04	100.53	100.79	-1.48%
09	98.01	99.39	98.70	100.21	101.07	100.64	-1.95%
10	98.80	100.14	99.47	100.52	101.14	100.83	-1.37%

Method 1 - Combined five tablets from each batch (a) and (b) for twin analysis (c) and (d) under numbers 1 – 4 Method 2 - Similarly combined one tablet from each batch for twin analysis in numbers 5 - 7. Method 3 - Similarly combined half a tablet from each batch for twin analysis in numbers 8-10.

Table V: Second laboratory based comparative single and twin batch assay results of paracetamol tablets (Current samples).

No	Assay % of two batches used for twin analysis		Average assay (A) = (a+b)/2	Twin batch duplicate assay % using same batches (a) and (b) combined			Deviation (A-B)
	Batch 1 (a)	Batch 2 (b)		Sample1 (c)	Sample2 (d)	Average assay (B) = (c+d)/2	
01	99.90	99.80	99.85	100.33	100.33	100.33	-0.48%
02	101.01	101.24	101.12	100.17	99.07	99.62	+1.48%
03	101.53	99.75	100.64	98.41	98.96	98.69	+1.93%
04	102.28	98.74	100.51	99.56	99.18	99.37	+1.13%
05	99.30	99.21	99.26	100.48	99.98	100.23	-0.98%
06	99.04	98.73	98.89	96.97	97.16	97.06	+1.85%

Method 1-Combined five tablets from each batch (a) and (b) for twin analysis (c) and (d) under numbers 1and 2. Method 2 – Similarly combined one tablet from each batch for twin analysis in numbers 3 and 4. Method 3 – Similarly combined half a tablet from each batch for twin analysis in numbers 5 and 6.

Table VI: Second laboratory based comparative single and twin batch assay results of paractamol tablets (Shelf samples).

No	Assay % of two batches used for twin analysis		Average assay (A) = (a+b)/2	Twin batch duplicate assay % using same batches (a) and (b) combined			Deviation (A-B)
	Batch1 (a)	Batch 2 (b)		Sample 1 (c)	Sample2 (d)	Average assay (B) = (c+d)/2	
01	97.20	99.90	98.55	98.80	97.80	98.30	+0.25%
02	98.80	100.56	99.68	99.79	99.04	99.42	+0.26%
03	101.44	101.83	101.64	102.20	101.22	101.21	+0.42%
04	100.14	100.55	100.34	99.62	99.06	99.34	+1.00%
05	100.14	100.56	100.35	100.52	100.57	100.55	-0.20%
06	100.14	97.20	98.67	100.19	99.95	100.07	-1.42%

Method 1-Combined five tablets from each batch (a) and (b) for twin analysis (c) and (d) under numbers 1 and 2. Method 2 – Similarly combined one tablet from each batch for twin analysis in numbers 3 and 4. Method 3 – Similarly combined half a tablet from each batch for twin analysis in numbers 5 and 6.

Table VII: Assay results of the blinded sample analysis.

Powder sample No	Assay %		Average blinded Assay %	Expected blinded assay %	% deviation
	Sample1	Sample 2			
01	99.15	100.08	99.62	100	-0.38%
02	50.34	49.04	49.69	50	-0.31%
03	24.61	24.80	24.71	25	-0.29%

Table VIII: Comparative single and twin batch dissolution test results of paractamol tablets (Current and shelf samples).

Sample type	Individual dissolution% values of two batches used for twin analysis				Twin batch analysis dissolution% values*	
	Batch 1		Batch 2		Min	Max
	Min (a)	Max (b)	Min (c)	Max (d)		
Current samples	98.56	100.07	99.06	103.09	102.33	106.61
	97.80	99.30	97.55	99.31	100.70	102.33
	97.80	99.82	99.31	102.08	101.71	103.34
	97.05	102.59	98.81	101.45	100.20	104.10
Shelf samples	102.08	104.73	101.96	102.97	99.31	103.22
	101.83	103.09	93.90	101.95	101.58	103.34
	99.82	100.45	99.57	100.57	99.57	102.96
	102.71	103.21	100.83	104.97	101.96	104.60

**Twin batch dissolution performed combing half a tablet from each batch. See figure 1 for twining procedure flow chart.*

Table IX: Second laboratory based comparative single batch and twin batch dissolution test results of paractamol tablets (Current and shelf samples).

Sample type	Dissolution% of two batches used for twin analysis				Twin batch analysis dissolution% values*	
	Batch 1		Batch 2		Min	Max
	Min (a)	Max (b)	Min (c)	Max (d)		
Current samples	99.31	102.08	99.06	103.09	100.34	101.01
	97.80	99.82	98.81	101.45	98.11	100.56
Shelf Samples	99.44	100.82	98.64	100.32	100.38	101.67
	100.19	100.83	102.71	103.21	99.20	101.45

**Twin batch dissolution performed by combing half a tablet from each batch to be twined. See figure 1 for twining procedure flow chart.*

Table X: Comparative single and twin batch friability test results of paractamol tablets (Current and shelf samples).

Sample Type	Friability % values of two batches used for twin analysis		Average friability	Twin batch friability %	Deviation
	Batch 1	Batch 2			
Current Samples	0.19	0.37	0.28	0.19	0.09%
	0.11	0.15	0.13	0.08	0.05%
Shelf Samples	0.26	0.23	0.24	0.15	0.09%
	0.26	0.23	0.24	0.14	0.10%

Table XI: Comparative single and twin batch hardness test results of paractamol tablets (Current and shelf samples) in Kilopascal.

Sample	Hardness of two batches used for twin analysis		Average A = (a+b)/2	Twin batch hardness values			Deviation A –B
	Batch1 (a)	Batch2 (b)		Min	Max	Average	
Current samples	11.21	10.84	11.02	9.9	13.3	11.97	- 0.95%
	10.30	10.90	10.60	10.9	13.4	11.83	-1.23%
Shelf samples	9.50	9.80	9.65	10.2	13.2	11.58	-1.93%
	9.77	9.80	9.78	10.6	12.4	11.12	-1.34%

Table XII: Single batch analysis of the viable microbial colony counts.

Sample		Bacterial colony count after 24 h incubation at 34 ^{0}C		Fungal colony count after 48 h incubation at 25 ^{0}C
		Observation	Dilution factor adjustment (X 10)	
Current samples	Sample 1	1	10	None
	Sample 2	0	0	None
Shelf samples	Sample 1	2	20	None
	Sample 2	2	20	None
Control		0	0	None

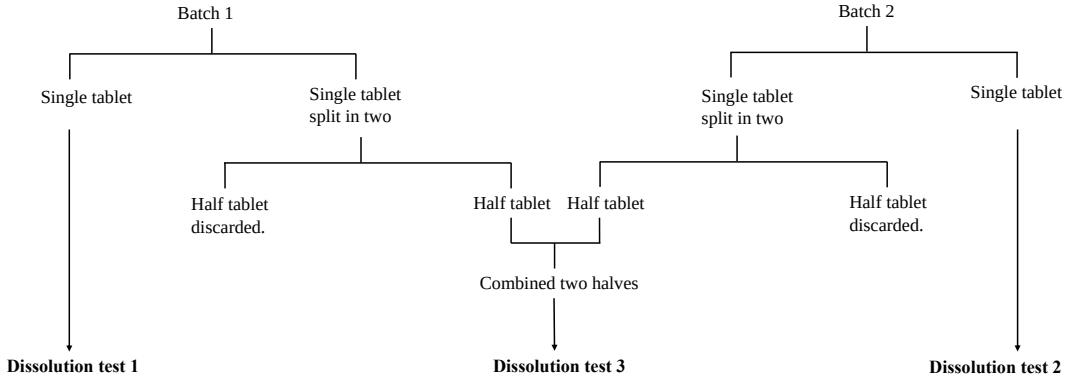

Figure I: Flow chart representing twin batch dissolution test undertaken in the present study.

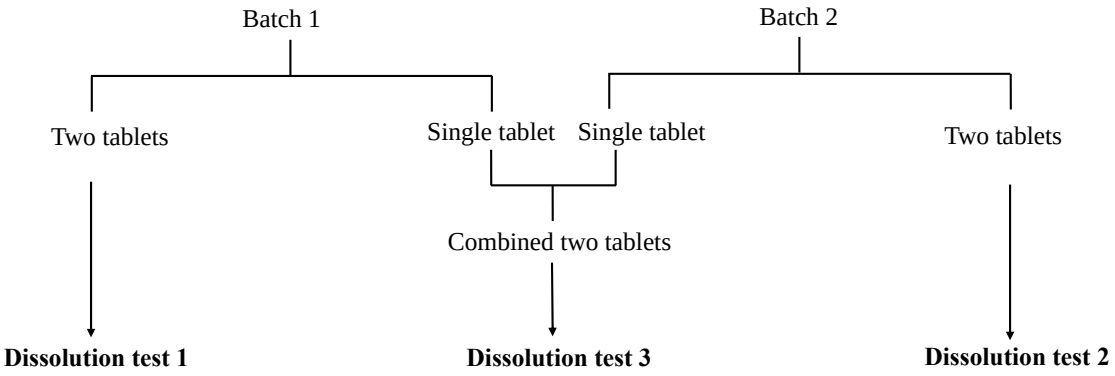

Figure 2: Flow chart representing proposed alternative twin batch dissolution test.

DISCUSSION

The Twin Batch Analysis Protocol was intended to provide a substantial measure of relief in performing a large number of repeated analyses of selected well established products manufactured in a large number of batches. Implementation of the TBAP scheme is possible only in an environment of sound quality assurance and good manufacturing practices. The main focus of the study is the possibility of reproducing comparable results in the twin batch analysis to that of constituent single batches involved in the twining process.

Eight criteria for the selection of a candidate product for the TBAP had been set out under introduction. The protocol covering a very wide area of analytical settings will effectively expose any possible weaknesses of the product quality. Assessment of data in 120 analyses of batches manufactured over an eight years period in table 1 and further analyses of 56 and 40 samples in tables 3 and 4 provide a comprehensive data coverage for the TBAP study. Examination of the tables will show that no less than fifteen different parameters had been studied in establishing the protocol for paracetamol tablets. These settings may have to be altered for other products depending on the active ingredient and dosage characteristics. For instance, if there is a limit test for a by-product this test has to be included in the TBAP study.[14]

The completed TBAP dossier of a given product has to be submitted to the regulatory authorities either for approval or for information before adopting the process routinely for the purpose of releasing the product to the market.

Under the twin batch analysis process, if the specifications are met the results are valid for both the twined batches. If any one of the specifications fail to comply, then the entire twin batch analysis results have to be discarded and each of the two twined batches must be analysed independently by the conventional methods. TBAP must be withheld until a thorough investigation is undertaken for the deviation and the problem identified. The TBAP procedure could be easily adapted to both manual and automated analytical procedures (1).

In addition to the weight variation of the tablets, the weight variation test for half a tablet was also conducted (Table 2).[15] According to the results, half tablet weight variation test of current samples, as well as the shelf samples, have complied the specifications. This implies that the tablets have been properly divided through the break line.[16]

Table 3 illustrates a comparison between individual batch assay values (a, b, A) and actual twin batch assay values (c, d, B) for current samples. The majority of the assay values were within 98%-101% range. The shelf samples in table 4 show similar results. Combined assay results of tables 3 and 4 show that TBAP could be adopted for this parameter.

The second laboratory tests results for the current and shelf samples in tables 5 and 6 confirm that the assay results can be reproduced.

The blinded test was done to check the absence of any biases and procedural errors in analysis. It was carried out with three unknown powder samples of crushed tablets diluted with lactose coded No. 01, 02, and 03. Batch numbers and assay values were unknown to the analyst. Tablet weight was given as 560.00 mg. According to the table 7 blinded analysis test results complied accurately with sample strengths 100%, 50%, and 25% of label claim. The results indicate that the method used for the assay was accurate, the analyst was unbiased and most importantly if twining pair of batches were deficient in active ingredient content, that will be detected.

All dissolution test results are well above the cut off minimum value of 80%. Single batch and twin batch analysis values in the first and the second laboratories are quite similar for this important parameter (Tables 8 and 9).

Possible reletive increase in dissolution due to exposed surfaces of the two tablet halves can be overcome as follows. Determine the dissolution of individual batches using two whole tablets for the test from each of the batches to be twined. For twining purpose, combining

one tablet from each of the above two batches and proceed with the test. (Figure 2) The sample strenght for calculation will be the strength of two tablets, 2 X 500 mg in this case. Friability and hardness test results too complies the TBAP requirements.

The method used to enumerate the microbial count was an in-house method followed by the manufacturer SPMC. Tablet samples from current and shelf samples were subjected to viable count determination. The maximum bacterial colony count was 20 per plate and for fungi it is nil (Table 12). All the values are well within the prescribed limits.

Some of the specific technologies that yielded consistently homogeneous tablets are the Class 100,000 clean zone, microbial viable count limits for clean zone air, tableting machine with facilities to prevent effects on tablet weight due to granule head changes, vibration free operation avoiding granule separation, feed frame with facilities for downward deflection of granules, extended cam for weight adjustment, pre-press for granule air elimination, the main press for the final punching and continuous display of compaction force by both presses.

CONCLUSION

The twin batch analysis project carried out here could be considered a useful validation process of the 'Twin Batch Analysis Protocol'. The qualifying criteria for the candidate product to be subjected to TBAP and the comprehensive nature of the study merits serious attention of the industry. For a rigorous determination, diverse test parameters and settings were undertaken in the protocol validation process. The inclusion of tests on freshly made and older batches representing two extremes of the shelf life, twining them under three different combinations in the number of tablets drawn, undertaking analysis in a second laboratory, blinded tests and tests involving tablet halves reflect the rigorous nature of validation process. The blinded twin batch analysis has confirmed the credibility of this protocol. The 50% reduction in the analytical workload of a high throughput product under TBAP can be diverted to quality assurance work related to Good Manufacturing Practices and greater attention to quality control of other products.

On these grounds, it may be concluded that the proposed TBAP with reference to paracetamol tablets used here should be acceptable both to the industry and regulatory bodies. On the basis of this model, the protocol could be adapted to other dosage forms. The TBAP must be an integral part of the product dossier and should be subjected to all regulatory requirements and events related to the product dossier.

No Twin Batch Analysis Protocol should be adopted unless all applicable parameters setout here are carried out.

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CONFLICT OF INTEREST

None.

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