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REPRODUCIBILITY DETERMINATION OF OPTIMIZED BATCHES OF ACECLOFENEC AND QUETIAPINE FUMARATE SPHERICAL CRYSTALS BY COMPARING THE DISSOLUTION PROFILES EMPLOYING THE SIMILARITY AND DISSIMILAR FACTORS

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ABSTRACT
The objective of this study was to check reproducibility of spherical crystals of optimized batches of aceclofenac and quetipine fumarate by a comparative study of dissolution profiles. The statistical comparison of the dissolution profiles was carried out by Moore and Flanner proposed model independent mathematical approach using two factors, dissimilar factors (f1) and similarly factor (f2). It was found that the optimized batches of spherical crystals of both drugs are close to each other.

Key words: *Dissimilar factors (f1), Similarly factor (f2), Dissolution, Spherical Crystals, Drug powder*

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INTRODUCTION

Drug absorption from a solid dosage form like tablet and capsule after oral administration depends on the release of the drug substance from the dosage form. To validate the extend of drug absorption taking place dissolution study is required. In the presence of certain minor changes, the single-point dissolution study may be adequate to ensure the reproducibility of the product but when there are chances of major changes, the dissolution profile comparison may be carried out by using a model independent or a model dependent method (1). In the recent years, FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers (2).

Under the appropriate test conditions, a dissolution profile can characterize products more precisely than using a single point dissolution test.

Among the several methods investigated for dissolution profile, it was found that a simple model independent approaches uses a difference factor (f1) and a similarity factor (f2) was useful in dissolution comparative study which was proposed by Moore and Flanner (1,3)

$$f1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100 \quad (1)$$

$$f2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\} \quad (2)$$

Where n is the number of times points, Rt and Tt are the cumulative percentage dissolved at each of

the selected n time points of the reference and test product respectively.

In dissolution profile comparisons, especially to assure similarity in product performance, pharmaceutical interest is in knowing how similar the two curves are, and to have a measure which is more sensitive to large differences at any particular time point. For this reason, the f2 comparison has been the focus in agency guidance.

Notice that f2 =100 when the two dissolution profiles are identical and an average difference of 10% at all measured time point results in an f2 value of 50. The FDA has set a standard of f2 ≥ 50%, to indicate similarity between two dissolution profiles (4)

The dissolution measurements of the two products (test and reference, pre- and post- change, two strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same (2,4)

MATERIALS AND METHODS

The *in vitro* dissolution test of aceclofenac & quetiapine fumarate, and of their spherical crystals (5) of batches were carried out using USPXXIV Paddle type (USP II) dissolution rate apparatus (Electrolab Tablet Dissolution Tester TDT - 60P) using 900 ml of pH 7.4 phosphate buffer in 37 ± 0.5^{o}C at 50 rpm. 5 ml of aliquots were withdrawn at suitable time interval using syringe filter sartorius grade 393 with replacement. The aliquots of aceclofenac and quetiapine fumarate were analyzed spectrophotometrically at 275.4, 248.20 nm respectively and dissolution profiles were compare by using equation 1 and 2 and similarity and dissimilarity factors was calculated. The second approach was used to determine the factors, in this approach, the optional weight (w) was calculated by taking the ratio of the absolute difference of the percentage of drug dissolved between reference (R) and test (T) formulation (6)

RESULTS

Similarity Factors (F2)

Table 1: Similarity Factors (f2) for Aceclofenac drug powder and its Spherical Crystals (Batch FAC1)

S.No.	Time (Minute)	Cumulative Drug Release (%)		$(R_t-T_t)^2$	Similarly factor (f2)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	**0**	**27.94**
2.	5	5.09	11.92	46.65	
3.	10	7.16	16.53	87.80	
4.	15	9.22	24.32	228.01	
5.	30	10.33	38.16	774.51	
6.	45	13.83	56.92	1856.75	
7.	60	24.01	72.66	2366.82	
8.	75	41.34	83.32	1762.32	
9.	90	58.83	89.99	970.95	
10.	105	71.71	94.13	228.01	
11.	120	91.11	97.95	46.79	
		$\Sigma_{t=1}^{n} (R_t-T_t)^2 = 8368.60$			

Table 2: Similarity factors (f2) for Aceclofenac drug powder and its Spherical Crystals (Batch FAC2)

S.No.	Time (minute)	Cumulative Drug Release (%)		$(R_t-T_t)^2$	Similarly factor (f2)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	
2.	5	5.09	11.17	36.97	
3.	10	7.16	16.21	81.90	
4.	15	9.22	22.92	187.69	
5.	30	10.33	39.21	834.05	
6.	45	13.83	57.92	1943.93	
7.	60	24.01	73.67	2466.12	**27.33**
8.	75	41.34	82.98	1733.89	
9.	90	58.83	89.72	954.19	
10.	105	71.71	95.09	546.62	
11.	120	91.11	98.13	49.28	
		$\Sigma_{t=1}^{n} (R_t-T_t)^2 = 8834.64$			

Table 3: Similarity factors (f2) for Quetiapine Fumarate drug powder and its Spherical Crystals (Batch FQT1)

S.No.	Time (Minute)	Cumulative Drug Release (%)		$(R_t-T_t)^2$	Similarly factor (f2)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	
2.	5	6.09	13.92	61.31	
3.	10	9.15	19.53	107.74	
4.	15	12.02	27.20	230.43	
5.	30	15.32	37.06	472.63	
6.	45	17.72	53.91	1309.72	
7.	60	32.15	68.66	1332.98	
8.	75	54.47	83.32	832.32	**33.19**
9.	90	68.85	89.99	446.90	
10.	105	78.17	97.13	359.48	
11.	120	95.01	98.95	15.52	
		$\Sigma_{t=1}^{n} (R_t-T_t)^2 = 5169.03$			

Table 4: Similarity factors (f2) for Quetiapine Fumarate drug powder and its Spherical Crystals (Batch FQT2)

S.No.	Time (Minute)	Cumulative Drug Release (%)		$(R_t-T_t)^2$	Similarly factor (f2)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	
2.	5	6.09	12.98	47.47	
3.	10	9.15	19.17	100.40	
4.	15	12.02	28.12	259.21	
5.	30	15.32	38.18	522.58	
6.	45	17.72	52.87	1235.52	

7.	60	32.15	69.59	1401.75	**32.90**
8.	75	54.47	84.76	917.48	
9.	90	68.85	90.78	480.92	
10.	105	78.17	95.96	316.48	
11.	120	95.01	98.46	11.90	
		$\Sigma_{t=1}^{n} (R_t-T_t)^2 = 5293.71$			

Table 5: Comparison of Similarity Between batches (FAC1 & FAC2) of Spherical Crystal of Aceclofenac

S.No.	Batch	Similarly factor (f2)
1.	FAC1	27.94
2.	FAC2	27.33

Table 6: Comparison of Similarity Between batches (FAC1 & FAC2) of Spherical Crystal of Aceclofenac

S.No.	Batch	Similarly factor (f2)
1.	FQT1	33.19
2.	FQT2	32.90

DISSIMILARITY FACTORS (f1)

Table 7: Dissimilarity factors (f1) for Aceclofenac drug powder and its Spherical Crystals (Batch FAC1)

S.No	Time (Minute)	Cumulative Drug Release (%)		$\lvert R_t-T_t \rvert$	Dissimilarity factor (f1)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	
2.	5	5.09	11.92	6.83	
3.	10	7.16	16.53	9.37	
4.	15	9.22	24.32	15.10	
5.	30	10.33	38.16	27.83	
6.	45	13.83	56.92	43.09	
7.	60	24.01	72.66	48.65	**76.14**
8.	75	41.34	83.32	41.98	
9.	90	58.83	89.99	31.16	
10.	105	71.71	94.13	22.42	
11.	120	91.11	97.95	6.84	
	$\Sigma_{t=1}^{n} R_t$ =332.63		**$\Sigma_{t=1}^{n} \lvert R_t-T_t \rvert$ =253.27**		

Table 8: Dissimilarity factors (f1) for Aceclofenac drug powder and its Spherical Crystals (Batch FAC2)

S.No	Time (Minute)	Cumulative Drug Release (%)		$\lvert R_t-T_t \rvert$	Dissimilarity factor (f1)
		Drug Powder(R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	
2.	5	5.09	11.17	6.08	
3.	10	7.16	16.21	9.05	
4.	15	9.22	22.92	13.70	
5.	30	10.33	39.21	28.88	

6.	45	13.83	57.92	44.09	**76.48**
7.	60	24.01	73.67	49.66	
8.	75	41.34	82.98	41.64	
9.	90	58.83	89.72	30.89	
10.	105	71.71	95.09	23.38	
11.	120	91.11	98.13	7.02	
	$\Sigma_{t=1}^{n} R_t$ =332.63		**$\Sigma_{t=1}^{n} \lvert R_t-T_t \rvert$ =254.39**		

Table 9: Dissimilarity factors (f1) for Quetiapine Fumarate drug powder and its Spherical Crystals (Batch FQT1)

S.No	Time (Minute)	Cumulative Drug Release (%)		$\lvert R_t-T_t \rvert$	Dissimilarity factor (f1)
		Drug Powder (R_t)	Spherical Crystal (T_t)		
1.	0	0	0	0	**51.60**
2.	5	6.09	13.92	7.83	
3.	10	9.15	19.53	10.38	
4.	15	12.02	27.20	15.18	
5.	30	15.32	37.06	21.74	
6.	45	17.72	53.91	36.19	
7.	60	32.15	68.66	36.51	
8.	75	54.47	83.32	28.85	
9.	90	68.85	89.99	21.14	
10.	105	78.17	97.13	18.96	
11.	120	95.01	98.95	3.94	
	$\Sigma_{t=1}^{n} R_t$ =388.95		**$\Sigma_{t=1}^{n} \lvert R_t-T_t \rvert$ =200.72**		

Table 10: Dissimilarity factors (f1) for Quetiapine Fumarate drug powder and its Spherical Crystals (Batch FQT2)

S.No	Time (Minute)	Cumulative Drug Release (%)		$\lvert R_t-T_t \rvert$	Dissimilarity factor (f1)
		Drug Powder (R_t)	Spherical crystal (T_t)		
	0	0	0	0	**51.90**
	5	6.09	12.98	6.89	
	10	9.15	19.17	10.02	
	15	12.02	28.12	16.10	
	30	15.32	38.18	22.86	
	45	17.72	52.87	35.15	
	60	32.15	69.59	37.44	
	75	54.47	84.76	30.29	
	90	68.85	90.78	21.93	
	105	78.17	95.96	17.79	
	120	95.01	98.46	3.45	
	$\Sigma_{t=1}^{n} R_t$ =388.95		**$\Sigma_{t=1}^{n} \lvert R_t-T_t \rvert$ =201.92**		

Table 11: Comaprision of Dissimilarity Between Batches (FAC1 & FAC2) of Spherical Crystal of Aceclofenac

S.No.	Batch	Similarly factor (f2)
1.	FAC1	76.14
2.	FAC2	76.48

Table 12: Comaprision of Dissimilarity Between batches (FQT1 & FQT2) of Spherical Crystal of Quetiapine Fumarate

S.No.	Batch	Similarly factor (f2)
1.	FQT1	51.60
2.	FQT2	51.90

DISCUSSION:

The similarity factors (f2) of both drug's (aceclofenac and quetiapine fumarate) spherical crystals were calculated and compared. It was found that similarity values of both batches of aceclofenac spherical crystals are close to each other so no significant difference in the dissolution profile. The same results were observed in the case quetiapine fumarate spherical crystals. It was also found that the similarity values are more than 50 so the spherical crystals of both drug's batches are identical which indicates reproducibility.

The dissimilarity factors (f1) of both drug's (Aceclofenac and Quetiapine Fumarate) spherical crystals were calculated and compared. It was found that dissimilarity values of both batches of aceclofenac spherical crystals are close to each other so no significant difference in the dissolution profile can be noted. The similar finding were also observed in the case quetiapine fumarate spherical crystals so spherical crystals of optimized batches are identical and reproducible

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