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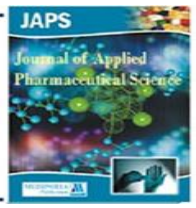

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Process optimization of efavirenz film coated tablet

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ABSTRACT

Optimization is often used in pharmacy relative to formulation & processing and one may find it in literature referring to any study of formula. Optimize means to make a perfect, effective (or) functional as possible. Process optimization is the discipline of adjusting a process so as to optimize some specified set of parameters without violating some constraint. The most common goals are minimizing cost, maximizing output, and/or efficiency. This is one of major quantitative tools in industrial decision making. In the present work process parameters at developmental stages of formulation were studied extensively and after completion of the data generated during the Process Optimization of Efavirenz tablets , some critical parameters were identified and some changes are recommended in various stages of manufacturing process and finally proved that process is capable of producing a drug of required quality with proposed process.

Key words: Optimization , Blending, Shifting, Mixing, Turret, Dissolution.

INTRODUCTION

Process optimization is the discipline of adjusting a process so as to optimize some specified set of parameters without violating some constraint. The most common goals are minimizing cost, maximizing out put, and/or efficiency. This is one of major quantitative tools in industrial decision making. In today's market optimization requires skill in understand in physico chemical properties of their materials and effect on the process identification and dependent and independent variables and understanding of expected relationship between cause and effect is crucial to the success of this approach (Agraval et al., 2006) The trail and error approach is more time consuming and often provides an approximately acceptable formulation and process. Optimization may be employed in process development laboratory sent by Technology transfer department. The aim is to get optimized formula and a process in a laboratory stage to develop the most stable product (Clark et al.,2001). Different methods like Evolutionary operations ,the Simplex method, the Langrangain method, Search method are present for optimization. The present study was done by search method. This technique is also known as non parametric search method, and is relatively simple, used to optimize a process by varying the critical process parameters which found during performing various trails done by process development department in co-ordination with technology transfer department (Bhandari et al.,2006). The main objective of this work is to optimize the process of Efavirenz 600 mg film coated tablet. Every drug has to be optimized and validate before going for manufacturing of them in large scale. (Egreman.,1994) The work aims at fixing variables of process which results in better quality granules with required characteristics.The present work aims at optimizing process variables for Efavirenz 600 mg film coated tablet. Herbert A et al., 1998) Reasons for optimization is to evaluate and generate the data to conform the process parameters can be varied during process optimization, so that final product

at pilot scale will produce consistent results. Materials used in present study are Efavirenz, Microcrystalline cellulose, Sodium Lauryl Sulphate, Croscarmellose sodium, Hydroxy Propyl Cellulose, Lactose Monohydrate, Magnesium Sterate, Opadry yellow, Purified water.

METHODOLOGY

Following trials were performed in the present study.

Sifting:(Trial 1, Trial 2, Trial 3, Trial 4 ,Trial 5)

Sieve Efaverinz, lactose monohydrate, microcrystalline cellulose and croscarmellose sodium separately through #20 mesh, Hydroxy propyl cellulose was sifted through 30 mesh. Sodium Lauryl Sulphate was sifted through 60 mesh.

Dry mixing: (Trial 1)

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried out up to 15 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate after 5, 10, 15 minutes of mixing intervals and submitted for analysis. (Huang Y et al.,2003)

Dry mixing: (Trial 2, Trial 3, Trial 4 ,Trial 5)

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried for 10 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate and submitted for analysis

Granulation: (Trial 1)

The granulating fluid was added over a period of 2 minutes with impeller at slow speed. Kneading was done with impeller and chopper at slow speed for 30seconds, followed by impeller and chopper at fast speed for 30 seconds.

Granulation: (Trial 2, Trial 3, Trial 4 ,Trial 5)

The granulating fluid was added over a period of 2 minutes with impeller at slow speed. Kneading was done with impeller and chopper at slow speed for 1 minute, followed by impeller and chopper at fast speed for 30 seconds

Drying: (Trial 1, Trial 2, Trial 3, Trial 4 ,Trial 5)

Drying was carried out at an inlet temperature of 60^0 C ± 5^0 C in fluidised bed dryer till the loss on drying of granules is 1.25– 2.25 % w/w.

Sifting and milling: (Trial 1)

Dried granules are sifted through #20 mesh and retentions milled through multi mill using 1.5mm screen at slow speed, knives forward direction. Milled granules were sifted through #20mesh and retentions were milled through 1.5mm screen at medium speed, knives forward direction and sifted through #18 mesh.

Sifting and milling: (Trial 2)

Dried granules are sifted through #18 mesh and retentions milled through multi mill using 1.5mm screen at slow speed, knives forward direction. Milled granules were sifted through #20Smesh and retentions were milled through 1.5mm screen at medium speed, knives forward direction and sifted through #20 mesh.

Sifting and milling: (Trial 3, Trial 4 ,Trial 5)

Dried granules are sifted through #24 mesh and retentions milled through multi mill using 1.5mm screen at slow speed, knives forward direction. (Jingshan Ren et.al.,2005)Milled granules were sifted through #24 mesh and retentions were milled through 1.0mm screen at slow speed, knives forward direction and sifted through #24 mesh.

Extra granular materials sifting: (Trial 1, Trial 2, Trial 3, Trial 4 ,Trial 5)

Lactose monohydrate, magnesium stearate were sifted through #40 mesh.

Blending (Prelubrication): (Trial 1)

Load the sifted and milled granules and Lactose monohydrate octagonal blender(Jiraporn Chingunpituk et al.,2007)and mix up to 15 minutes. 10 point unit dose samples collected in duplicate after 5, 10 and 15minutes of mixing interval and submitted for analysis.

Blending (Prelubrication): (Trial 2, Trial 3, Trial 4 ,Trial 5)

Load the sifted and milled granules and talc, Lactose monohydrate into octagonal blender and mixed for 10 minutes. 10 point unit dose samples collected and submitted for analysis.

Blending (Lubrication): (Trial 1)

Load Magnesium stearate to the pre lubricated materials in octagonal blender and blend for 3min, 5 min and 7 min

Blending (Lubrication): (Trial 2, Trial 3, Trial 4 ,Trial 5)

Load Magnesium stearate to the pre lubricated materials in octagonal blender and blend for 3min.

Compression: (Trial 1,Trial 2, Trial 3, Trial 4 ,Trial 5)

Compression of Efavirenz tablets were done as per the specifications.

RESULTS AND DISCUSSION

In the trail 1 the drymixing is carried out for 5, 10, 15 minutes. Based on the r.s.d the drymixing time is optimised to 10 minutes. In the table 1 the trails 1,2 and 5 were represented where trail 1,2 shows the results of various timing for optimisation and the trail 5 which shows the best dry mixing time.In the trail 1 the prelubrication is carried out for 5, 10, 15 minutes. Based on the r.s.d the drymixing time is optimised to 10 minutes.In the table 2 the trails 1 and 5 were represented where trail 1 shows the results of various timing for optimisation and the trail 5 which shows the best pre lubrication time.In the trail 1 the prelubrication is carried out for 3, 5, 7 minutes. Based on the r.s.d the drymixing time is optimised to 3 minutes.In the table 3 the trails 1 and 5 were

Table 1 Dry mixing optimization for different trail batches.

BATCHES	Trail 1 (Percentage label claim)			Trail 2	Trail 5
	5 minutes	10 minutes	15 minutes	10 minutes	10minutes
1	100.7	101.0	102.1	103.3	100.9
2	102.8	101.5	101.5	101.9	100.0
3	102.7	101.5	100.7	102.1	100.1
4	100.7	102.0	101.0	103.4	100.1
5	101.2	101.4	102.8	100.2	100.0
6	101.8	100.8	100.9	103.4	98.9
Average	101.7	101.4	101.5	102.4	100.0
Minimum	100.7	100.8	100.7	100.2	98.9
Maximum	102.8	102.0	102.8	103.4	100.9
R.s.d	0.94	0.42	0.81	0.98	0.6

Table 2 Pre lubrication optimization for different trail batches.

Location	Trail 1 (Percentage label claim)			Trail 5
	5 minutes	10 minutes	15 minutes	10 minutes
1	99.5	100.6	99.1	98.5
2	98.6	101.2	99.2	99.7
3	101.1	100.2	99.3	99.9
4	99.9	99.5	99.6	100.1
5	99.1	100.3	99.8	99.9
6	101.2	99.7	99.7	99.8
7	99.6	99.7	99.3	100.6
8	100.9	99.7	99.8	99.7
9	100.1	99.9	100.0	97.9
10	100.2	100.6	99.9	100.7
Average	100.02	100.14	99.57	99.88
Minimum	98.6	99.5	99.1	97.9
Maximum	101.2	101.2	100.0	100.7
R.S.D	0.86	0.54	0.32	0.59

Table 3 Pre-lubrication optimization for different trail batches.

Location	Trail 1 (Percentage label claim)			Trail 5
	3 minutes	5 minutes	7 minutes	3 minutes
1	97.7	105	108	99.5
2	99.3	101.2	105	100.8
3	100.1	103	103	99.8
4	99.7	93	93	100.3
5	100.9	102.2	102.2	98.1
6	100.7	95	95.0	100.4
7	97.1	104.4	104.4	97.9
8	100.4	100.4	100.4	101.4
9	97.4	103.1	103.1	99.3
10	99.3	93	103	100.8
Average	99.3	100.03	101.71	99.83
Minimum	97.1	93	93	97.9
Maximum	100.9	104.4	108	101.4
R.s.d	1.39	4.62	4.54	1.15

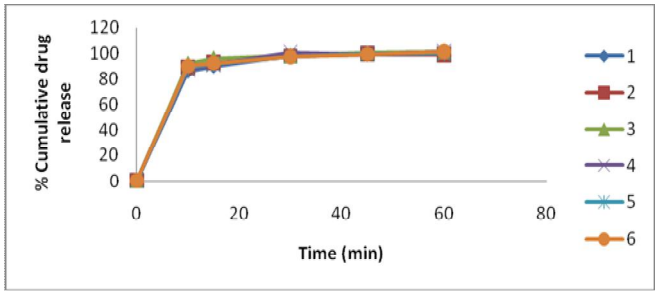

Fig 1 Invitro dissolution studies of efaverinz(trail 2).

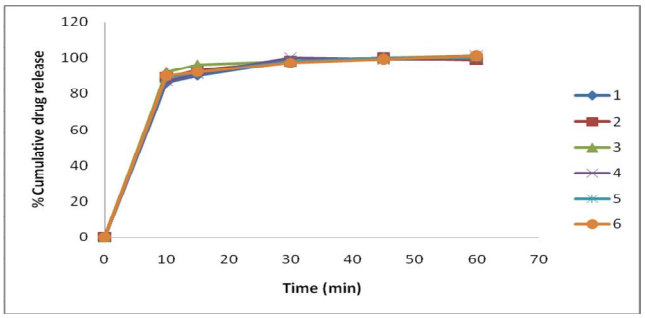

Fig 2 Invitro dissolution studies of efavirenz(Trail 3).

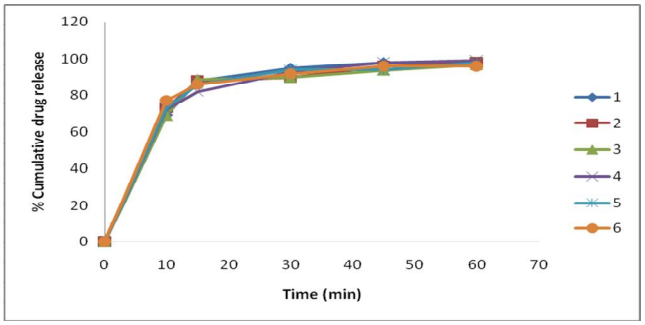

Fig 3 Invitro dissolution studies of efavirenz(Trail 4 - turret 20 rpm).

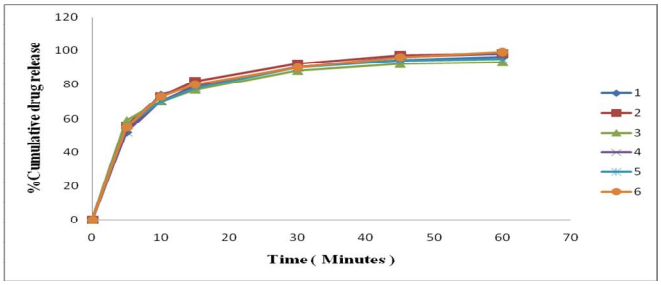

Fig 4 Invitro dissolution studies of Efavirenz(Trail 4 - turret 25 rpm)

Table 4 Tablet compression parameters at different turret speeds

Trail	Average weight (mg)		Uniformity of weight (mg)		Thickness (mm)		Hardness (kp)		Disintegration Time (min)		Friability (% w/w)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Limits	(1176.00 - 1224.00 mg)		± 5 % of average weight		(7.30 –7.90 mm)		(18.0 – 29.0 kp)		NMT 15 Minutes		NMT 1.0	
4 (20 rpm)	1187	1216..3	1188.5	1214.6	7.62	7.91	17.4.	27.5	8’	10’4”	0.01	0.14
4 (25 rpm)	1190.6	1214.9	1196.8	1221.9	7.74	7.98	20.4	28.0	7’	10’07”	0.05	0.06
4 (30 rpm)	1174.0	1226.0	1191.9	1225.4	7.80	7.97	19.4	28.8	6”	9’07’’	0.07	0.12
5 (20-25 rpm)	1192.0	1212.0	1198.3	1212.6	7.80	7.87	18.1.	26.5	7’	10’04”	0.05	0.07

Tablet 5 Invitro dissolution studies of Efavirenz (Trail 2).

Unit no.	%Cumulative drug release					
	0 minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	0	56	58	63	67	74
2	0	51	60	65	68	73
3	0	57	60	65	66	72
4	0	54	59	64	70	75
5	0	60	65	69	72	74
6	0	58	63	67	73	73
Mean	0	56	59	65	68	72
Minimum	0	51	60	63	65	70
Maximum	0	60	63	69	73	74

Tablet 6 Invitro dissolution studies of efaverinz(Trail 3).

Unit no.	%Cumulative drug release					
	0 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	0	80	88	96	98	98
2	0	87	93	100	101	99
3	0	80	84	92	92	93
4	0	79	85	92	93	93
5	0	80	85	92	92	94
6	0	79	86	94	95	95
Mean	0	81	87	94	95	95
Minimum	0	79	84	92	92	93
Maximum	0	87	93	100	101	99

Tablet 7 Invitro dissolution studies of efavirenz (Trail 4 - turret 20 rpm).

Unit no.	%Cumulative drug release					
	0 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	0	69	88	95	98	98
2	0	73	88	90	96	98
3	0	69	89	90	94	97
4	0	72	82	93	98	99
5	0	73	86	94	94	98
6	0	77	86	92	96	96
Mean	0	72	87	92	96	98
Minimum	0	69	82	90	94	96
Maximum	0	77	89	95	98	99

Tablet 8 Invitro dissolution studies of efavirenz(Trail 4 - turret 25 rpm).

Unit no.	%Cumulative drug release					
	0 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	0	74	79	90	94	96
2	0	73	82	92	97	98
3	0	70	77	88	92	93
4	0	70	79	90	96	98
5	0	70	78	90	94	95
6	0	73	80	90	96	99
Mean	0	72	79	90	95	97
Minimum	0	70	77	88	92	93
Maximum	0	74	82	92	97	99

represented where trail 1 shows the results of various timing for optimisation and the trail 5 which shows the best lubrication time.

The compression of the tablets is done at different turret speeds of 20 rpm, 25 rpm, 30 rpm in the trail 4.When the compression is done at 30 rpm turret speed the weight variation is seen thus the turret speed of 20 – 25 rpm is set as the optimum turret speed for compression of the tablet. (Kimberly et al 2000) The trail 5 results

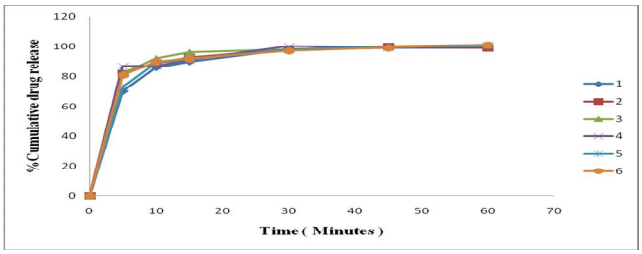

Fig 5 Invitro dissolution studies of efavirenz (Trail 5).

Tablet 9 Invitro dissolution studies of efaverinz (Trail 5).

Unit no.	Cummulative drug release					
	0 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	0	86	90	98	99	99
2	0	89	93	98	100	99
3	0	92	96	98	100	101
4	0	87	91	100	99	101
5	0	89	92	98	100	100
6	0	90	92	97	99	101
Mean	0	89	92	98	100	100
Minimum	0	86	90	97	99	99
Maximum	0	92	96	100	100	101

has shown the best results.Dissolution is carried out in 900 ml Purified water dissolution medium of pH 2.0 in USP apparatus II, paddle with 50 rpm.The release of the drug efaverinz is good in the trail 3,4 and 5. Trail 5 has show the optimum dissolution values.

CONCLUSION

The following changes are recommended in various stages of manufacturing process for executing the Test batch / Pilot scale batches.

- Dry mixing, pre lubrication, lubrication time optimization
- Kneading time increased to overcome the sticking problem
- Change of mesh and sieves to overcome the dissolution problem
- Turret speed is optimized to 20 – 25 rpm

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