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DEVELOPMENT AND PROCESS OPTIMIZATION OF SOLID DOSAGE FORM (CYCLOBENZAPRINE HYDROCHLORIDE) FROM LAB SCALE TO PILOT SCALE

VEERAMANIKANDAN V[*1], SOUMEN PATTANAYEK[2] AND KATHIRESAN K[3]

1: Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India

2: Director, Research & Development, Teva Pharmaceuticals USA, Inc. 2843 Oakbrook Drive, Weston, FL, 33332

3: Associate Professor, Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India

***Corresponding Author: Veeramanikandan V: E Mail: veeramanicdm2020@gmail.com;**

Mobile: 9786763820

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ABSTRACT

Objective: To develop and to perform process optimization of solid dosage form (Skeletal muscle relaxant) from lab scale to pilot scale. To do the following tests on newly formulated Cyclobenzaprine Hydrochloride tablet and do Weight variation test, Thickness test, Hardness test and Friability test.

Method: Dry granulation is typically used in the manufacture of tablets if the formulation ingredients are too fluffy or too susceptible to flowability problems for direct compression to be a viable processing option and/or too susceptible to degradation from heat and/or moisture for wet granulation to be a viable processing option for densification. The process is sometimes

chosen as an alternative to wet granulation when direct compression is not feasible not because wet granulation is not feasible but because the manufacturer is more experienced with dry granulation or to reduce processing time and/or equipment requirements to reduce costs. The direct compression method is used.

Result: The formulation 5 (F5) - It passes the weight variation test, thickness test, hardness test and friability test mainly the formulation-5 with coating 2% give best results in the above tests.

Conclusion:

- The prepared Cyclobenzaprine Hydrochloride tablet formulation 5 (F5-2%) passes the limits of weight variation test, thickness test, hardness test and friability test.
- So far the formulation-5 (F5-2%) coated 2% is the best one for the pilot scale production of Cyclobenzaprine Hydrochloride tablet 10mg.

Keywords: Direct compression, Tablet coating, Weight variation test, Hardness test, Friability test, Uniformity of thickness, Dry granulation

INTRODUCTION

Tablets are the most accepted drug delivery systems for oral administration. They are convenient to manufacture on a large scale with reproducibility, stability and have high patient acceptability. The major drawback of conventional tablets is need of frequent administration to maintain therapeutically effective concentration of drug in blood. Conventional oral drug products, such as tablets and capsules release the active drug for oral administration to obtain rapid and complete systemic drug absorption. However fluctuations in plasma concentration below MEC lead to loss of therapeutic activity **[1-3]**.

To maintain the therapeutic concentration required for its effect, next dose has to be immediately administered. An alternative to administering another dose is to use a dosage form that will provide a sustained drug release, and therefore maintain plasma drug concentrations within therapeutic range for longer duration **[4-7]**.

Pharmaceutical dosage forms have been developed to release active substances in modified manner as compared with conventional formulations **[8]**. Modification in release of active substances may have a number of objectives but the main intention is to maintain therapeutic activity without frequent dosing, reduce toxic effect and reduce the work load of the patient **[9, 10]**.

The European Pharmacopoeia defines modified release in terms of the rate or the

site at which the active ingredient is release **[11]**. A modified-release dosage form is defined as "A formulation of medicinal drug taken orally, releases the active ingredients over several hours in order to maintain a relatively constant plasma concentration of the drug'' **[12-14]**.

MATERIAL AND METHODS

The materials used in this solid dosage (skeletal muscle relaxant) are cyclobenzaprine hydrochloride, lactose monohydrate, pregelatinized starch, hydroxyl propyl cellulose (flakes), hydroxyl propyl cellulose (LXF), colloidal silicon dioxide, magnesium stearate **(Table 1)**.

Methods Used

Lab scale production

In lab scale production dry granulation method is used.

Dry granulation

Dry granulation is typically used in the manufacture of tablets if the formulation ingredients are too fluffy or too susceptible to flowability problems for direct compression to be a viable processing option and/or too susceptible to degradation from heat and/or moisture for wet granulation to be a viable processing option for densification **[15-17]**. The process is sometimes chosen as an alternative to wet granulation when direct compression is not feasible not because wet granulation is not feasible but because the manufacturer is more experienced with dry granulation or to reduce processing time and/or equipment requirements to reduce costs **[18-20]**.

Direct compression method

It is performed by using 10-station instrumented Piccola tablet press at 30rpm 9/32" Std. round concave **[21]**. The processing of drug with excipients can be achieved without any need of granulation and related unit operations. By simply mixing in a blender, formulation ingredients can be processed and compressed into tablets without any of the ingredients having to be changed. This procedure is called direct compression and it is used in the manufacture of tablets when formulation ingredients can flow uniformly into a die cavity **[22-24]**.

Evaluation of tablet

The prepared tablet was subjected to the optimization process to test the quality of them. Here we produced five types of formulation to predict the best one.

The five types of formulations are prepared and it used to make tablet by direct compression method **(Table 2)**.

Table 1: Ingredients used in tablet formulation

S.NO	INGREDIENTS	USED AS	VENDER
1	Cyclobenzaprine hydrocholoride	Active pharmaceutical ingredient	Hetero drugs limited GummadidalaMandal, Telangana.
2	Lactose monohydrate	Fillers and stabilizing agent	DMV-Fonterra Excipients GmbH & Co, Germany.
3	pregelatinized starch	Diluent and disintegrant	Colorcon, Indianappolis, Indiana;U.S.A
4	Hydroxy propyl cellulose (Flaxes)	Binder	Ashland speciality ingredients GP, Hopewell, Virginia.
5	Hydroxy propyl cellulose (LXF)	Additional Binder	Ashland speciality ingredients GP, Hopewell, Virginia.
6	Colloidal silicon dioxide	Glidant	CABOT Sanmar limited, Plant-v, Raman Nagar, Mettur dam, Salem.
7	Magnesium stearate	Lubricant	Peter Greven Nederland CV, Fdisonstroat, The Nederland.
8	Opadry Yellow	Coloring agent	Colorcon Asia private limited, Goa.
9	Water	For making coloring agent	IH

Table 2: F1 to F5 formulation

Granulation process: Direct mixing process							
S.no	INGREDIENTS	F1(mg/tab)	F2(mg/tab)	F3(mg/tab)	F4(mg/tab)	F5(mg/tab)	
1	Cyclobenzaprine Hcl	10.00	10.00	10.00	10.00	10.00	
2	Lactose monohydrate	121.62	121.62	120.12	119.75	112.25	
3	pregelatinized starch	5.00	5.00	10.00	10.00	15.00	
4	HPC (Flakes)	10.00	-	-	-	-	
5	HPC (LXF)	-	10.00	7.50	7.50	10.00	
6	Colloidal silicon dioxide	3.00	3.00	2.00	2.00	2.00	
7	Magnesium stearate	0.38	0.38	0.38	0.75	0.75	
	Core tablet weight	150.00	150.00	150.00	150.00	150.00	
1	Opadry yellow	Q.S	12% concentration			Q.S	Q.S
2	Purified water	Q.S					
	Coated tablet weight	154.5	-	-		153	154.5

RESULT AND DISCUSSION

(i) Weight variation test:

Table 3: Average weight of tablets for F1 to F5

S.no	F1(mg/tab)	F2(mg/tab)	F3(mg/tab)	F4(mg/tab)	F5(mg/tab)	F1(Coated)	F5(Coated)
1	147	150	147	150	152	154	157
2	146	147	154	151	150	156	155
3	150	146	153	152	156	156	152
4	153	154	146	147	151	152	158
5	149	149	150	156	146	155	153
6	154	151	152	154	147	153	154
7	156	156	151	153	149	154	156
8	151	150	156	149	153	159	155
9	152	153	150	146	154	154	159
10	150	154	148	150	152	152	156
Total weight	1508	1510	1507	1508	1510	1545	1555
Average weight	150.8	151	150.7	150.8	151	154.5	155.5

Percentage deviation = 7.5

Table 4: Weight variation for F1 to F5

S. No	Formulation	Lower weight	Higher weight
1	F1	-3.28	3.33
2	F2	-3.42	3.20
3	F3	-3.21	3.39
4	F4	-3.28	3.33
5	F5	-3.42	3.20
6	F1 (Coated-3%)	-2.36	2.13
7	F5 (Coated-2%)	-2.30	2.20

Table 5: SD values for F1 to F5

S. No	Formulation	Average weight of 10 tablets	Mean ±SD(mm)
1	F1	150.8	±0.53
2	F2	151	±0.66
3	F3	150.7	±0.46
4	F4	150.8	±0.53
5	F5	151	±0.66
6	F1 (Coated-3%)	154.5	±2.91
7	F5 (Coated-2%)	155.5	±3.53

- **The mean ±SD (mm) for the F1 to F5 lies between ±0.53 to ±3.53mm**

(ii) Thickness values for core tablet in mm:

Table 6: Thickness values for core tablet in mm

S. No.	F1	F2	F3	F4	F5
1	3.26	3.15	3.13	3.16	3.22
2	3.29	3.18	3.16	3.19	3.25
3	3.27	3.20	3.26	3.22	3.26
4	3.29	3.17	3.28	3.31	3.23
5	3.31	3.19	3.17	3.18	3.24
6	3.32	3.22	3.24	3.20	3.26
7	3.30	3.21	3.27	3.15	3.25
8	3.33	3.23	3.14	3.17	3.24
9	3.28	3.16	3.15	3.30	3.23
10	3.34	3.24	3.29	3.33	3.27

Thickness limits: 3.0 to 3.5mm. Therefore , thickness of the core tablet parameter are lies between; 3.26 – 3.34mm for the formulation 1 (F 1); 3.15 – 3.24mm for the formulation 2 (F2); 3.13 – 3.29mm for the formulation 3 (F3); 3.16 – 3.33mm for the formulation 4 (F4); 3.22 – 3.27mm for the formulation 5 (F5)

Thickness test value for coated tablet in mm:

Table 7: Thickness test value for coated tablet in mm

S.NO	F1 (3%)	F2	F3	F4	F5 (2%)
1	3.28	Coating not done due to bad disintegration report.	Coating not done due to presence of picking.	Coating not done due to presence of sticking.	3.15
2	3.30				3.20
3	3.29				3.21
4	3.35				3.25
5	3.31				3.26
6	3.33				3.22
7	3.32				3.24
8	3.29				3.19
9	3.34				3.17
10	3.36				3.27

Thickness limits: 3.0 to 3.5mm. Therefore the thickness of the coated tablet is lies between, 3.28 – 3.36mm for the formulation 1 (F1-3%); Coating is not done for the formulation 2 (F2) due to improper result of disintegration in core tablet itself; Coating is not done for formulation 3 (F3) due to presence of picking; Coating is not done for formulation 4 (F4) due to presence of sticking; 3.15 – 3.27mm for formulation 5 (F5-2%)

(iii) Hardness value for core tablet in N:

Table 8: Hardness value for core tablet in N

S. No.	F1	F2	F3	F4	F5
1	52.6	50.5	55.2	51.6	49.3
2	55.0	55.0	55.3	53.4	50.2
3	54.0	60.2	60.8	56.0	54.6
4	60.5	77.0	58.9	57.5	56.7
5	63.0	68.0	62.3	62.7	59.7
6	65.0	54.0	67.6	65.4	60.4
7	67.4	83.4	74.7	67.8	51.9
8	68.2	85.4	65.0	52.9	53.8
9	60.0	86.0	57.7	70.6	59.6
10	69.8	87.2	75.6	71.7	60.8

Hardness limits: 40 to 100N.Therefore, hardness of the core tablet parameters lies between; 52.6 – 69.8N for the formulation 1 (F1); 50.5 – 87.2N for the formulation 2 (F2); 55.2 – 75.6N for the formulation 3 (F3); 51.6 – 71.7N for the formulation 4 (F4); 49.3 – 60.8N for the formulation 5 (F5)

Hardness test for coated tablet in N:

Table 9: Hardness test for coated tablet in N

S.No.	F1 (3%)	F2	F3	F4	F5(2%)
1	72	Coating process not done due to bad disintegration result.	Coating not done due to presence of picking	Coating process not done due to presence of sticking.	76.1
2	75.3				78.6
3	74				79.2
4	77.1				77.5
5	82.5				80.5
6	86				84.2
7	89				87.0
8	79				88.3
9	88.2				89.4
10	92				90.8

Hardness limits: 40 to 100N. Therefore the hardness result for the coated tablet lies between;

- **72 – 92N for the formulation 1 (F1-3%); Coating process not done for formulation 2 (F2) due to bad disintegration process; Coating process not done for formulation 3 (F3) due to presence of picking; Coating process not done for formulation 4 (F4) due to presence of sticking; 76.1 – 90.8N for the formulation 5 (F5-2%)**

(iv) Friability test values for F1 to F5

Table 10: Friability test values for F1 to F5

Formulation number	Friability %
F1	0.45
F2	0.16
F3	3.2
F4	2.5
F5	0.69

Friability test was carried out and found that it was 0.45% for formulations F-1, 0.16% for F-2, 3.2% for formulation F-3, 2.5 for formulation F-4 and 0.69 % for formulation F-5. It evidence that formulation F-1 and F-5 passes the test as per IP limit of less than 1 %.

CONCLUSION

- The prepared Cyclobenzaprine Hydrochloride tablet 10mg formulation 5 (F5-2%) passes the limits of Weight variation test, thickness test, hardness test and friability test.

- So far the formulation- 5 (F5) coated 2% is the best one for the pilot scale production of Cyclobenzaprine Hydrochloride tablet 10mg.
- Because formulation- 5 (F5) coated 2% passes all the limits.

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