IJBPAS, February, 2021, 10(2): 584-592

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DEVELOPMENT AND PROCESS OPTIMIZATION OF SOLID DOSAGE FORM (SKELETAL MUSCLE RELAXANT) FROM LAB SCALE TO PILOT SCALE

VEERAMANIKANDAN V* AND KATHIRESAN K

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

***Corresponding Author: Veeramanikandan V: E Mail: veeramanicdm2020@gmail.com; Mobile: +91-9786763820**

Received 17th April 2020; Revised 29th May 2020; Accepted 29th July 2020; Available online 1st Feb. 2021

https://doi.org/10.31032/IJBPAS/2021/10.2.5369

ABSTRACT

Objective: To develop and to perform process optimization of solid dosage form (Skeletal muscle relaxant) from lab scale to pilot scale. To done the following tests on newly formulated Cyclobenzaprine Hydrochloride tabletand done Disintegrationand Dissolution 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 disintegration test and also it give best dissolution values because it gradually release the drug Cyclobenzaprine Hydrochloride on the formulation-5 (coated 2%) and in core tablet state itself also.

Conclusion: The prepared Cyclobenzaprine Hydrochloride tablet formulation 5 (F5) passes the limits of disintegration and dissolution tests.

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

Because it passes all the limits and it give 105.0% of drug release in 45 minutes on dissolution studies.

Keywords: Direct compression, Tablet coating, Dissolution test, Disintegration test, 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)**.

Table 1: Ingredients used in tablet formulation

S. No	INGREDIENTS	USED AS	VENDER
1	Cyclobenzaprine hydrocholoride	Active pharmaceutical ingredient	Hetero drugs limited Gummadidala Mandal, 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

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 **(Table 2)**.

The below five types of formulations are prepared and it used to make tablet by direct compression method.

Table 2: F1 to F5 formulation

Granulation Process: Direct mixing process						
S. No	**Ingredients**	**F 1 (mg/tab)**	**F 2 (mg/tab)**	**F3 (mg/tab)**	**F 4 (mg/tab)**	**F 5 (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

Disintegration test values for core tablet in minutes (Table 3):

Therefore the disintegration time period for the core tablet parameters lies between;

- 3 mins 12 sec to 4 mins 15 sec for the formulation 1 (F1)
- 11 mins 52 sec to 15mins 12 sec for the formulation 2 (F2)
- 3 mins 20 sec to 4 mins 58 sec for the formulation 3 (F3)
- 3 mins 32 sec to 4 mins 46 sec for the formulation 4 (F4)
- 3 mins 30 sec to 4 mins 32 sec for the formulation 5 (F5)

Disintegration test (mins) for coated tablet is shown in **Table 4**.

Therefore disintegration results for the coated tablets are

- 3 mins 40 sec to 5 mins 30 sec for the formulation 1 (F1)
- Coating is not done in formulation 2 (F2) due to bad response in disintegration study in core tablet study itself.
- Coating is not done in formulation 3 (F3) due to presence of picking in disintegration study in core tablet study itself.
- Coating is not done in formulation 4 (F4) due to presence of impact in the core tablet study itself.
- 4 mins 30 sec to 5 mins 52 sec for the formulation 5 (F5)

Dissolution values (%) for reference tablets RLD1, RLD2, and RLD3 (Table 5).

Among them the reference drugs (RLD 1 and RLD2) both are gave good result as like that the pms RLD also gave good dissolution result mainly gradually increase the dissolution value **(Figure 1)**.

Dissolution test (%) values for F1 to F5 is shown in Table 6.

Among them the core tablet (F1), core tablet (F5) and coated tablet 3% (F5) fails the dissolution studies. Due to improper release of drug Cyclobenzaprine Hydro-chloride **(Figure 2)**.

Therefore the dissolution results are **(Figure 3)**,

- The coated tablet formulation 1 (F1-3%) gives good result in the dissolution study because it gradually increase the drug value. It release 94.8% of drug at 45 minutes.
- For the formulation 2 (F2) we can't able to done the dissolution study because it fails the disintegration study in the core tablet state itself.
- For the formulation 3 (F3) we can't able to done the dissolution study because it shows picking.
- For the formulation 4 (F4) it shows good dissolution study because in 45 mins it's release 101.6% of drug.
- The coated tablet formulation 5 (F5-2%) shows best drug release in the dissolution study because in 45 mins it release 105.0% of drug so it is the best formulation.

Table 3: Disintegration test values for core tablet in minutes

S. No.	F1	F2	F3	F4	F5
1	3mins 12 sec	11 mins 52 sec	3 mins 20 sec	3 mins 32 sec	3 mins 30 sec
2	3 mins 20 sec	11 mins 59 sec	3 mins 30 sec	3 mins 35 sec	3 mins 45 sec
3	3 mins 26 sec	12 mins 10 sec	3 mins 45 sec	3 mins 45 sec	3 mins 55sec
4	3 mins 50 sec	12 mins 33sec	3 mins 46 sec	3 mins 55 sec	4 mins 10 sec
5	3 mins 55 sec	13 mins 10 sec	3 mins 55 sec	3 mins 55 sec	4 mins 10 sec
6	4 mins 6 sec	13 mins 16 sec	4 mins 15 sec	4 mins 10 sec	4 mins 15 sec
7	4 mins 8 sec	13 mins 20 sec	4 mins 29 sec	4 mins 34 sec	4 mins 18 sec
8	4 mins 10 sec	15 mins 4 sec	4 mins 30 sec	4 mins 40 sec	4 mins 20 sec
9	4 mins 12 sec	15mins 10 sec	4 mins 48 sec	4 mins 44 sec	4 mins 30 sec
10	4 mins 15 sec	15 mins 12 sec	4 mins 58 sec	4 mins 46 sec	4 mins 32 sec

Table 4: Disintegration test (mins) for coated tablet

S. No.	F1	F2	F3	F4	F5
1	3 mins 40sec	Coating not done due to bad disintegration result.	Coating not done due to presence of picking	Coating process not done due to presence of impact.	4 mins 30 sec
2	3 mins 55 sec				4 mins 44 sec
3	3 mins 58 sec				4 mins 54 sec
4	4 mins 10 sec				4 mins 59 sec
5	4 mins 20 sec				5 mins 10 sec
6	4 mins 36 sec				5 mins 23 sec
7	4 mins 49 sec				5 mins 30 sec
8	4 mins 57 sec				5 mins 37 sec
9	5 mins 26 sec				5 mins 45 sec
10	5 mins 30 sec				5 mins 52 sec

Table 5: Dissolution values for reference tablets RLD1, RLD2, and RLD3

Time (mins)	RLD1 (%)	RLD2 (%)	RLD3 (%)
5	15.0	15.6	20.2
10	43.2	45.7	63.3
15	83.1	83.9	97.8
20	98.3	96.5	101.3
30	99.3	98.0	102.2
45	97.2	98.8	103.1

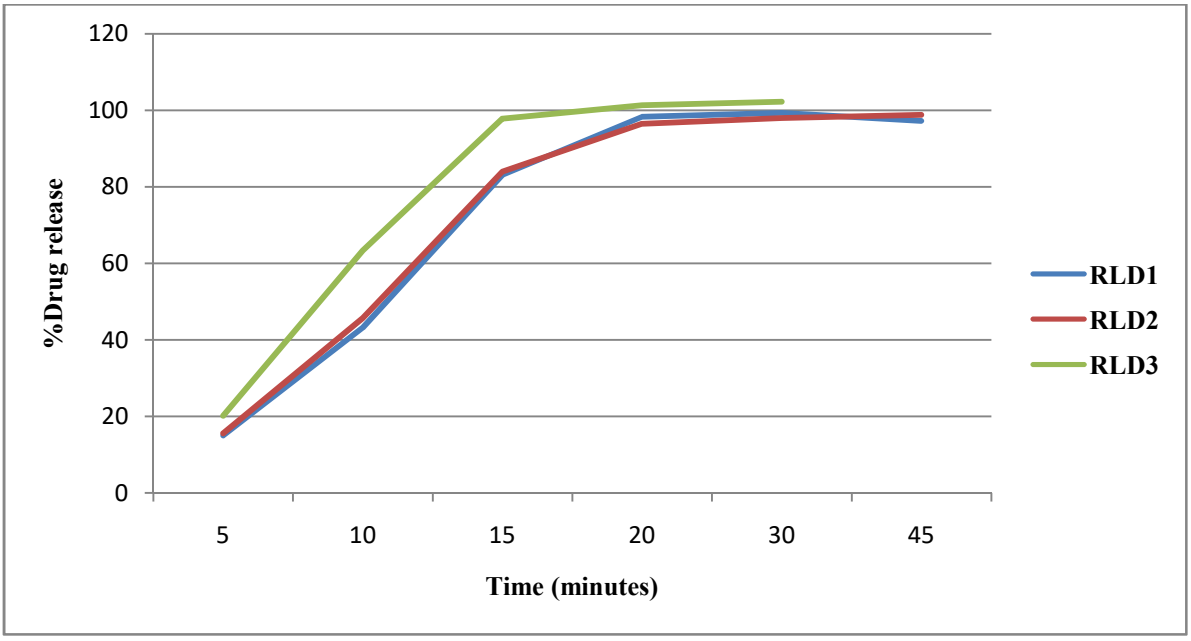

Figure 1: Graphical representation for dissolution values of reference tablets RLD1, RLD2, and RLD3

Table 6: Dissolution test values for F1 to F5

Time (mins)	F1		F2	F3	F4	F5		
	Core	Coated 3%			Core	Core	Coated 2%	Coated 3%
5	66.0	22.2	Not done due to bad disintegration result in core state itself.	Not done due to picking observed.	63.3	30.4	35.6	32.1
10	87.8	89.6			88.1	62.1	66.1	63.3
15	91.8	93.6			98.0	85.5	84.7	80.3
20	93.6	93.5			100.7	99.8	95.4	89.0
30	93.6	94.6			101.0	104.3	104.0	101.9
45	94.0	94.8			101.6	103.4	105.0	105.0

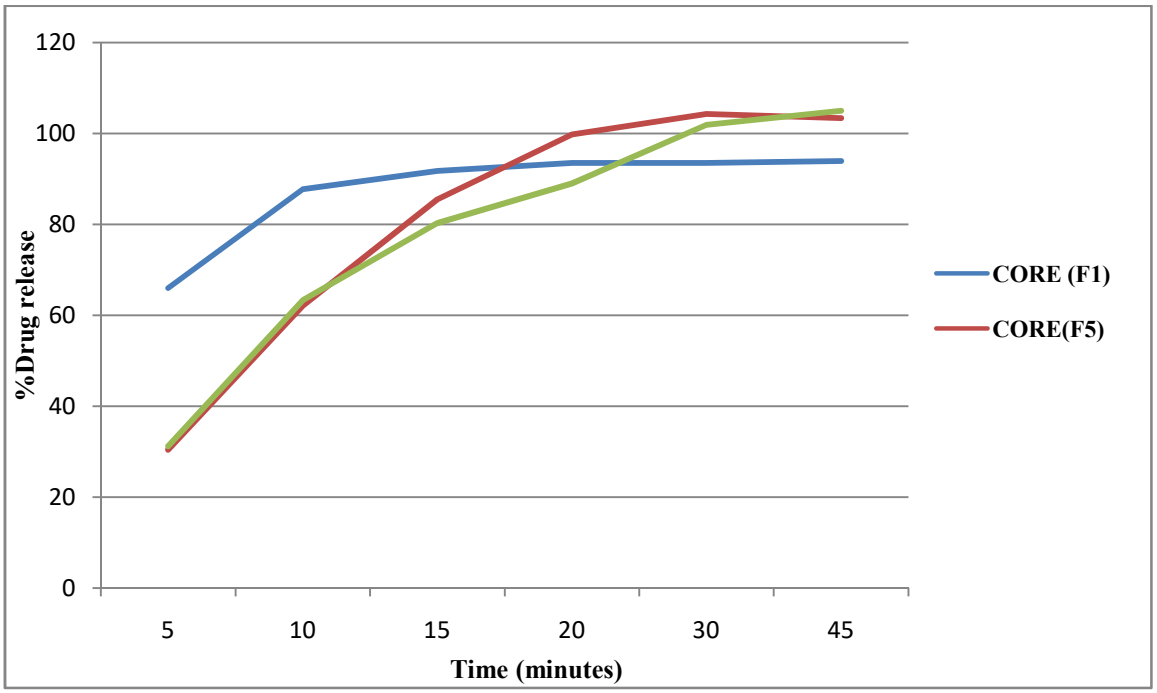

Figure 2: Graphical representation for dissolution test values for F1 to F5

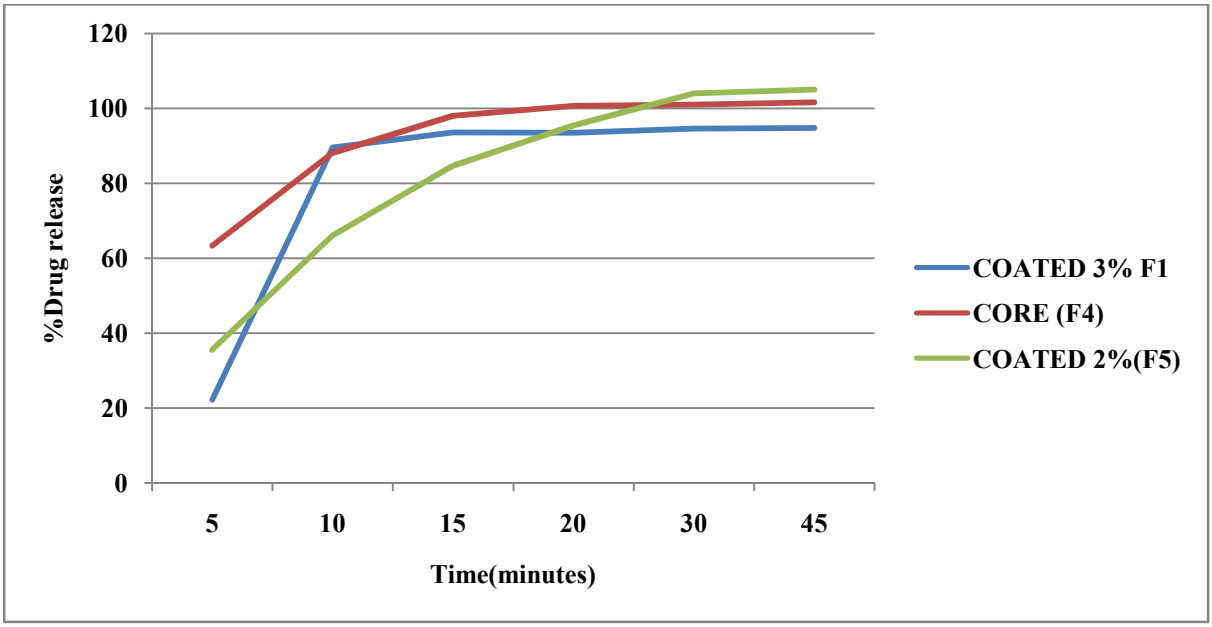

Figure 3: Graphical representation for formulations F1, F4 and F5

CONCLUSION

- The prepared Cyclobenzaprine Hydrochloride tablet 10mg formulation 5 (F5-2%) passes the limits of disintegration and dissolution studies.
- 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 and it gives 105.0% of drug release in 45 minutes on dissolution study.

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