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FORMULATION DEVELOPMENT AND EVALUATION OF CHEWABLE-DISPERSIBLE TABLET OF ANTI-EPILEPTIC DRUG

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ABSTRACT

Chewable-dispersible tablets are useful in patients, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attack, or coughing for those who have an active life style. The introduction of chewable dispersible dosage forms has solved some of the problems encountered in administration of drug to pediatric and elderly patients. The present investigation concerns the development of Chewable-dispersible tablets of lamotrigine which were designed to enhance the onset of action of lamotrigine. lamotrigine Chewable-dispersible tablet was prepared by using Crosspovidone XL10, as a disintegrating agent, different grades of mannitol (Pearlitol 160 C, Pearlitol SD 200, Pearlitol 500DC) as a diluents, PVP K30 as a binder and carried out studies for weight variation, thickness, hardness, content uniformity, disintegrating time, dispersion time, wetting time, in vitro drug release and stability study. Tablets were prepared by using direct compression method and wet granulation method. Furthermore, impact of different punches and superdisintegrants (Sodium Starch glycolate, and Sodium Crosscarmalose) were carried on F16 formulation.

Keywords: Chewable-dispersible tablets, disintegrating time, dispersion time, Sodium Starch glycolate.

INTRODUCTION

artial seizures, bipolar disorder, and in combination of other Anti-Epileptic drugs in different types of seizures. lamotrigine is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and pediatric and geriatric patients .

MATERIALS AND METHODS

Lamotrigine (LME01) procured by Alembic LtdIndia., Mannitol (Pearlitol 160 C), Mannitol

(Pearlitol 200 SD), Mannitol (Pearlitol 500 DC) procured by Signet chemical corporation,Mumbai, Aerosil USP/NF, Talc USP, Magnesium Stearate NF are purchased by Loba chemie,cochin.

DEVELOPMENT OF FORMULATION

Strategy was to formulate a chewable-Dispersible dosage form for LME01. It was assumed that chewable-Dispersible formulation for LME01 can be developed by compressing the drug and selected diluents into tablet formulation with the similar release profile as that of the Innovator Product. We were selected two strategies for formulation. 1) Direct compression 2) Wet granulation

DIRECT COMPRESSION:

Direct compression technique was very reliable, convenient, economic, reduces labor, less processing time and less process validation due to this reason direct compression technique was preferred. The trial was taken with directly compressible diluents like pearlitol 500 DC, pearlitol 160 C, pearlitol 200 SD, ludipress. It was also optimize the flavor and sweeteners concentration by giving it to selected volunteers.

Table No. 1: Composition of formulation from F1-F5 for direct compression

Ingredients	Batch No. Quantity per tablet ingredient (mg)				
	F1	**F2**	**F3**	**F4**	**F5**
LME01	25	25	25	25	25
Mannitol (Pearlitol 500 DC)	-	-	-	-	170.30
Mannitol (Pearlitol 200 SD)	-	-	-	159.80	-
Mannitol (Pearlitol 160 C)	165.05	164.00	96.90	-	-
Ludipress	-	-	80	-	-
Crosspovidone	8.4	8.4	6	10.5	10.5
Povidone (PVP K30)	6.3	6.3	-	10.5	-
Magnesium stearate	1.05	2.1	2.1	2.1	2.1
Talc	-	-	-	2.1	2.1
Colloidal silicone dioxide	4.2	4.2	-	-	-
Weight per tablet	210	210	210	210	210

WET GRANULATION

In direct compression strategy we observed that LME01 has not compressibility so we were made granules of LME01 with PVP K30, we added sodium saccharine into intra granulation. We were added aspartame and black current flavor in extra granulation.

Table No. 2: Composition of formulation from F6-F11 for wet granulation

Ingredients	Batch No.					
	Quantity per tablet ingredient (mg)					
	F6	F7	F8	F9	F10	F11
Intra granular						
LME01	25	25	25	25	25	25
Mannitol (Pearlitol 160 C)	-	81	164	155.60	76.855	20
Crosspovidone	5.25	-	-	8.4	8.4	8.4
Povidone (pvp k30)	4.2	4.2	8.4	8.4	8.4	8.4
Purified water	Qs	Qs	Qs	Qs	Qs	Qs
Extra granular	-	-	-	-	-	-
Mannitol (Pearlitol 160 C)	164	83	-	-	-	-
Mannitol (Pearlitol 500 DC)	-	-	-	-	78.74	135.60
Crosspovidone	5.25	10.5	8.4	8.4	8.4	8.4
Povidone (pvp k 30)	4.2	4.2	-	-	-	-
Magnesium stearate	2.1	2.1	2.1	2.1	2.1	2.1
Talc	-	-	-	2.1	2.1	2.1
Colloidal silicone dioxide	-	-	2.1	-	-	-
Weight per tablet	210	210	210	210	210	210

Optimization of sweeteners and flavor:

The optimization of sweeteners and flavors concentration of chewable dispersible tablets was prepared by using the two sweeteners, sodium saccharine and aspartame and flavor was black current. It was decided to use sweeteners and flavor in the chewable dispersible tablets as this formulation requires sweet taste and pleasant feeling in the mouth.

RESULT & DISCUSSION:

Impact of the different super disintegrants was shown in the table No 10 from that Crosspovidone was better than the SSG and Ac-Di-Sol due to the less disintegration and dispersion time of that formulation.

Rate and extent of dissolution of LME01 varied depending upon the type of excipient used (Table No: 11). From formulations containing pearlitol 500 DC and pearlitol SD 200, the amount dissolved was found to be satisfactory whereas from formulations containing ludipress was not found to be satisfactory when compared with dissolution profile of pearlitol 500 DC and SD 200. Results of Rate of dissolution were almost similar for formulations containing pearlitol 500 DC and pearlitol SD 200.As mannitol was hydrophilic in nature, release profile was found almost similar with all

its grade pearlitol 500 DC, pearlitol SD 200 and pearlitol 160 C. Here, disintegration time and dispersion time of pearlitol grade found similar but formulation containing Ludipress found higher DT and dispersion time compared to other formulation. As ludipress contain lactose, PVP K30 and Crosspovidone hardness was higher and taste of that formulation was not good.Formulation having F1, F2and F4 showed higher friability and capping of pearlitol grade 160 C, SD 200. But the formulation having pearlitol 500DC shown good dispersion pattern, optimum hardness due to coarser particle size.

In wet granulation technique it was formulated chewable dispersible tablets that were good compared to the direct compression. Pearlitol 500 DC as an extragranular material and pearlitol 160 C as a intragranular diluent give better formulation. We were optimized the intragranular and extragranular diluents. In all this formulation drug release profile was almost same but in the evaluation of the good formulation it has to be considering the disintegration time and dispersion time of the formulation. In the other formulation drug release profile was same but the DT and dispersion time was higher than F11 formulation. Formulation having F11 showed good disintegration time and dispersion time as well as friability and hardness into the range. This formulation was used for the impact of different punches.

It was used six different punches for the F11 formulation and checked the parameter. In the deep concave and standard concave punches was shown the friability issue and capping were observed during the evaluation. In P3 and P4 punches there was problem of getting punch chocking, on lower punch there was a layering of material so tablet ejection problem during compression was observed. Friability problem was observed and dispersion time was higher in both the punches of P3 and P4. In the P5 punch there was no friability and capping issue but during the dispersion time there was some hard mass was observed at last time. Here, it was obtained good result in the P6 punch and all the parameters were in the limit.

Comparison between Direct compression and Wet granulation:

First it was decided to go through the direct compression, but in the direct compression method some problems were encountered like poor flow property and fluffy nature of the drug flow of the blend material from the hopper was not proper due to that reason weight variation was observed that was solved in the wet granulation by granulating the drug.. Another problem was the tablet ejection from the die cavity that reason was due to the poor compressibility of the drug that problem was solved in the wet granulation by granulating the drug with the pvp k30 and made the granules compressible. In direct compression hardness and cracking of the tablet was the problem that

also solved in the wet granulation. In comparison of these two methods wet granulation was better method for this particular active. All the evaluation parameter of the wet granulation was better than direct compression.

Table No. 3: Results of Physical Characterization of F1-F5 for direct compression

Parameter	F 1	F 2	F 3	F 4	F 5
Uniformity of mass (mg)	210 ± 5	210 ± 3	210 ± 4	210 ± 3	210 ± 2
Hardness (Kp)	3-4 kp	3-4 kp	5-6 kp	3-4 kp	3-4 kp
Thickness (mm)	3.42	3.37	3.39	3.39	3.41
Friability (%)	1.23%	0.95%	0.23%	0.85%	0.63%
DT (second)	30	40	40-50	30	30-40
Dispersion time(sec)	45-60	40	30-40	40-45	30-40
Drug content (%)	97.56%	98.44%	96.16%	99.47%	99.88%
Wetting time (sec)	19	52	21	19	53

Table. No. 4:- Cumulative % release of F1-F5 for direct compression.

Batch / Time(Min)	F 1	F 2	F 3	F 4	F 5
5	97.60	96.71	92.56	97.11	96.32
10	99.70	99.30	95.71	99.43	100.49
15	99.70	100.23	97.22	100.71	100.62
20	99.70	100.23	97.22	100.71	100.62
30	99.70	100.23	97.22	100.71	100.62

Fig. No. 1: Dissolution profile of F1-F5 for direct compression

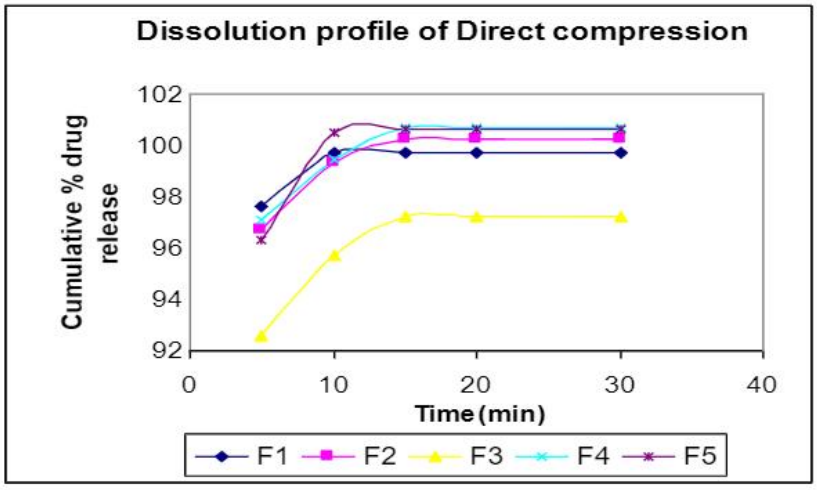

Table No. 5: Results of Physical Characterization of F6-F11 for wet granulation.

Parameter	F 6	F 7	F 8	F 9	F10	F 11
Uniformity of mass (mg)	210 ± 2	210 ± 5	210 ± 2	210 ± 3	210 ± 3	210 ± 1
Hardness (Kp)	2-3 kp	3-4 kp	5-6 kp	3-4 kp	5-6 kp	4-5 kp
Thickness (mm)	3.32	3.30	3.36	3.37	3.33	3.38
Friability (%)	0.90%	0.95%	0.43%	0.51%	0.47%	0.63%
DT (second)	40-45	40-50	40-50	50-55	50-60	30-40
Dispersion time(sec)	50-75	50-55	60-70	60-65	60-70	40-50
Drug content (%)	96%	99.10%	99.45%	98.63%	99.89%	100.12%
Wetting time (sec)	19	52	21	19	21	53

Table No. 6: Cumulative % release of F6-F11 for wet granulation.

Batch / Time(Min)	F 6	F 7	F 8	F 9	F10	F 11
30	100.21	100.11	99.87	101.21	101.19	100.54

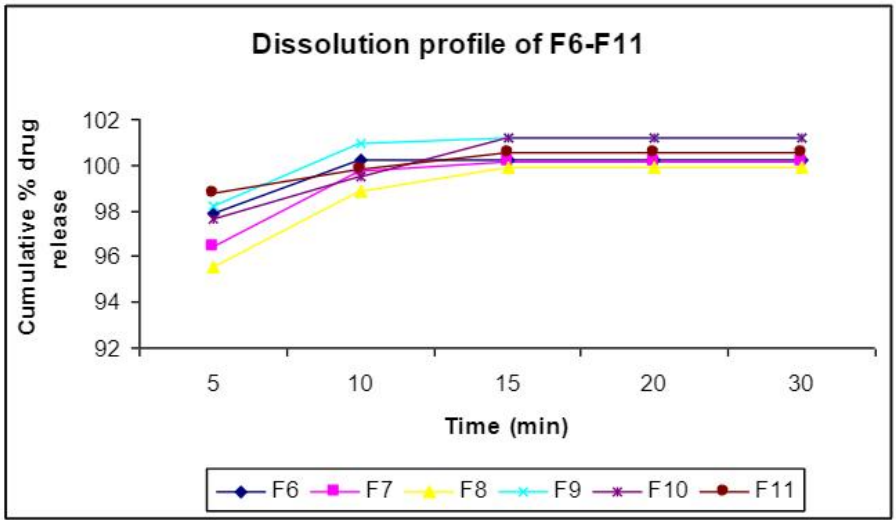

Fig. No. 2: Dissolution profile of F6-F11 for wet granulation

Table No. 7: Impact of punches on F11 formulation

Sr.No.	Ingredients	Quantity(mg)
	Intra granular	
1	LME01	25
2	Mannitol (Pearlitol 160 C)	20
3	Crosspovidone (Polyplasdone XL 10)	8.4
4	Povidone (Pvp k30)	8.4
5	Sodium saccharine	0.21
6	Purified water	Qs
	Extra granular	
7	Mannitol (Pearlitol 500 DC)	133.71
8	Crosspovidone	8.4
9	Black current flavor	0.63
10	Aspartame	1.05
11	Magnesium stearate	2.1
12	Talc	2.1
	Weight per tablet	210

Table No. 8 Evaluation Parameter

Sr.No	Parameter	P1	P2	P3	P4	P5	P6
1	Uniformity of mass (mg)	210 ± 2	210 ± 4	210 ± 3	210 ± 2	210 ± 3	210 ± 1
2	Hardness (Kp)	2-3 kp	2-3 kp	3-4 kp	4-5 kp	5-5.5 kp	4-5 kp
3	Thickness (mm)	3.61	3.52	3.59	3.41	3.36	3.20
4	Friability (%)	1.25%	1.08%	0.92%	1.21%	0.51%	0.42%
5	DT (second)	40-45	40-50	60-70	50-60	50-60	40-50
6	Dispersion time (sec)	50-60	50-60	120-130	120-130	60-70	40-50

Table No. 9: Impact of different super disintegrants on F16 formulation

Sr.No	Evaluation parameter	Results		
		With SSG	With Ac-Di-Sol	With Crosspovidone XL 10
1	Uniformity of mass (mg)	210 ± 2	210 ± 4	210 ± 3
2	Hardness (Kp)	4-5 kp	4-5 kp	4-5 kp
3	Thickness (mm)	3.61	3.59	3.58
4	Friability (%)	0.61%	0.60%	0.63%
5	DT (second)	50-60	60-70	30-40
6	Dispersion time(sec)	70-75	85-90	40-50

CONCLUSION

Chewable dispersible tablet for LME01 was developed and evaluated successfully using direct compression and wet granulation techniques. The problem of tablet ejection from compression machine was observed in direct compression due to the fluffy material of drug and particle size of the mannitol used in direct compression. We had used pearlitol 160 C, pearlitol SD200, pearlitol 500 DC in different formulation. In wet granulation the result was good but the problem of hardness and friability were encountered. Optimizing the formulation with pvp k30 and larger particle size of pearlitol 500 DC also solved that problem. We were concluding that wet granulation was good technique using the pearlitol 500 DC grade of mannitol for the formulation of chewable dispersible tablets.Further investigation on human volunteers for pharmacokinetic study is essential to bring out clearly the utility of these formulations for therapeutic uses.In the present study it was conformed that direct compression and wet granulation process can be used for manufacturing of chewable dispersible tablet of Anti-Epileptic Drug (AED) having more patient compliance and convenience. Due to many advantages of these two techniques chewable dispersible tablet can be commercialized to provide the advantages of liquid medication in the form of solid preparation.

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