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Research Article

DEVELOPMENT OF RAPID DISINTEGRATING MODIFIED RELEASE TABLET BY USING NOVEL PARTICLE COATING TECHNOLOGY

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ABSTRACT

The objective of present sturdy is to formulate rapid disintegrating modified release (RDMR) tablet of carbamazepine by using drug particle coating technology. Fluid bed granulation technology is most emerging and upcoming face of granulation technology of pharmaceuticals. The technology is used for granulation/agglomeration, layering, coating and drying of a wide range of particle size. The development of a polymer-based RDMR tablet was undertaken to produce a rapid disintegrating modified release dosage form of carbamazepine. Granulation and drug particle coating were performed by using fluidized bed technology using different polymeric combination (Eudragit RS 30D and HPMC P55) and retard the release rate of drug. Uniform particle coating was achieved by using the particle coating technology and Release rate was retarded. Rapid disintegration of tablet were achieved by using the extra-granular material with drug portion. Finally the Granular portion and extra granular portion with drug was blended and compressed, this was produced the RDMR tablet. Final compressed tablets were tested for Inprocess test and dissolution test based on the pharmacopoeial specifications. Shapes of the tablets were round, Weight variation, hardness, % friability, thickness, diameter, disintegration and dissolution tests were carried out for all the formulation and found within the pharmacopoeial specifications. Accelerated stability studies of the selected formulated tablets were carried out by keeping the tablets at 40°C ± 2°C / 75 ± 5% RH and 60°C ± 2°C / 75 ± 5% RH in stability ovens for 1 and 2 months.. All the parameters were checked and found within the limit after stability period. Selected formulations were compared with the marketed product and dissolution comparison study was performed with marketed formulation, found comparable. Nevertheless, the innovation of this article is to optimize all the Critical process parameters with respect to their quality attribute.

KEYWORDS: *Fluid-bed Technology, Top spray granulation, Process variables, Process analytical technologies.*

INTRODUCTION

In the pharmaceutical industry, most products are manufactured using the wet granulation process. Wet granulation offers a wide range of capabilities for forming granules, from the production of light granules to the production of very dense granules.

In addition to a simple fluid bed, the tumbling, agitating, centrifugal, and spiral flow fluid bed and the spouted bed with or without the draft tube have been developed for improving the process performance.

Among the many types of surface modification processes, the fluid bed processes are characterized with their easy, simple mechanical formation of multilayers on the particles [1].

Fluid bed granulation (FBG) is a process widely used in the manufacturing of solid pharmaceutical products. This unit operation has been extensively studied along the last decades, but due to its complexity, there is no general model that can be applied. FBG has two steps, the powders granulation (spraying phase) and the granules drying (drying phase). Both take place in only one vessel, a fluid bed dryer. In a particular process of this kind, which had been implemented long ago, it was intended to decrease the intrinsic variability that was observed on the granules quality by implementing the quality by design (QbD) concept [2].

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Fluid-bed Granulator:

The FBG, the most commonly used low-shear granulator and from the porous granules, uses a high volume of air flow to elevate powders in a chamber while a binding solution is sprayed onto the particles to form a light bond. A fluid-bed granulator does not impart mechanical energy but instead relies on the powder characteristics and the binding solution to form the lightly held powders into granules. A low-shear granulator will not produce a dense granule, and a high-shear granulator will not produce a light granule. Again, the objective must be understood before the granulation equipment is chosen [4].

Working Principle:

FBG work on the principle of fluidization, fluid bed forms when a fluidizing gas (e.g. air) flows through bulk material. Depending on the flow velocity of the gas, several different conditions must be defined.

At the beginning of the process, gas flows through a solid bed, i.e., stationary batch of particles. Starting from this initial state with a uniformly increasing airflow velocity, a point is reached at which the particles start moving and the product batch is fluidized. This point is referred to as fluidization point and marks the beginning of fluidization.

If the velocity is increased further, the particle movement also becomes more forceful. Air, which is not needed to maintain the particles in fluid state, passes through the fluid bed in the form of gas bubbles causing strong turbulence. The maximum flow rate is defined as the rate at which the particles are removed from the fluid bed by pneumatic conveyance. As turbulence in the fluid bed can be controlled, the particles mix very intensively. Also, the heat transfer between the gas and the solid material is very high. The same applies to the transfer of material. This makes the fluid bed technology the method of choice for drying and heat transfer processes [5].

"During top spray granulation, the powder particles circulate within the product chamber and provide a constant flow of bed particles through a defined spray granulation zone. At the spray granulation zone, a fine spray of liquid binder is usually atomized and deposited onto the fluidizing particles. Particle wetting brings about granule formation. Partial drying of the wetted particles by the fluidizing air occurs continuously during granulation. When the spraying of liquid binder is completed, the granules are quickly dried by the hot air stream and complete drying is achieved".

Theory of Fluidization:

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through at a rate fast enough to set them in motion. This velocity is higher than the incipient fluidizing velocity but lower than the entrainment velocity. When the rate of flow of air or gas is increase the pressure drop across the bed also increase until at a certain rate of flow the frictional drag on the particles equals the effective weight of the bed. This condition and the velocity of air or gas corresponding to them are termed incipient fluidization and incipient velocity respectively [7, 6].

As the velocity of the gas or air increases the bed continues to expand and its height increase with only slight increase in pressure drop. As the velocity of gas is further increased the bed continued to expand and its height increase whereas the concentration of particles per unit volume of bed decreases. At certain velocity of the fluidizing medium known as entrainment velocity, particles are carried over by the air or gas this phenomenon is called entrainment [8].

Carbamazepine (CBZ):

Carbamazepine (CBZ) is selected as a model drug for the study it is a first-line drug used for the treatment of partial and tonic-clonic seizures. It is also the drug of choice for use during pregnancy and recommended for the treatment of seizure disorders in children. CBZ possesses the ability to induce metabolism of drugs that are transformed in the liver and has the unique ability to induce its own metabolism by a phenomenon known as 'auto-induction', where its biological half-life is significantly reduced during chronic administration. Large doses of CBZ are often prescribed as daily divided doses and this often adversely affects patient compliance, with the result that therapy is ineffective. A sustained-release dosage form containing CBZ is currently marketed as Tegretol® CR [9].

MATERIALS AND METHODS

Materials:

Carbamazepine (CBZ) was obtained as gift sample and Eudragit RS 30D, HPMC P55, Triacetin, Talc, Microcrystalline Cellulose (PH 102), Crospovidone, Silica colloidal anhydrous, Magnesium stearate was obtained from different vendors.

Preparation of tablet:

Granulation:

Carbamazepine API particles were granulated by using fluidized bed processor using top spraying of suspension (Eudragit RS 30D, Talc, Triehyl citrate and purified water) onto the preheated material. During spraying monitor operation critically to avoid lump formation and ensure uniform Fluidization of material throughout the process. Spray second suspension (HPMC P55 with Ethanol+Acetone (60:40 Ratio) to the granulated blend during the proper fluidization of material and after drying and milling add the extragranuler material (Carbamazepine, Cellulose, Microcrystalline (PH 102), Croscarmellose sodium & Silica colloidal anhydrous) and blend it for 10 min and after addition of Magnesium stearate lubricate for 5 min [10-12].

Tablet compression:

Compression was performed on the compression machine fitted with Round shaped punches and check description, Average weight, Uniformity of weight, Hardness, Friability, Disintegration time and Thickness.

Process Optimization:

Based on the final optimized formulation and test results, final formula was taken for process optimization trials.

All the critical process parameters were optimize with respect to identifying the optimum range to use for better processing and reproducing the result oriented formulation.

Table No. 1: Optimization Plan - For Process

Process Parameters			
1.	Effect of Spray Rate	**6.**	Effect of Loss on Drying
2.	Effect of Product temperature	**7.**	Effect of Blending Time
3.	Effect of Hardness of Tablet	**8.**	Effect of Lubrication Time
4.	Effect of Atomization Pressure	**9.**	Effect of compaction force
5.	Effect of occupancy of equipment	**10.**	Effect of RPM

Evaluation of Tablets and Technical parameters:

Uniformity of weight:

Compressed tablet of the batch were tested for uniform weight and weight variation as per pharmacopoeia procedure. Weights were determined using Sartorious balance (Model CP-224 S). Weight control is based on a sample of 20 Tablets [13].

Dimensions:

The dimensions (diameter and thickness) were then determined by using vernier callipers and thickness and diameter of tables was evaluated.

Crushing strength:

The hardness of the Tablets was determined by using hardness tester (Model no 1101, Erweka). Tablet hardness was determined in triplicate.

Disintegration test:

The disintegration time (DT) of the Tablets was determined in distilled water at 37 ± 0.5 °C using disintegration test apparatus (Electrolab ED-2 Bowl USP, Mumbai). One Tablet was placed in each of the 6 tubes of the basket and the time taken for all the Tablets to disintegrate and go through the wire mesh was recorded. The disintegration time should not be more than 15 minutes.

Friability:

The friability of the Tablets was measured in a Roche friabilator. Tablets of a known weight (Wo) or a sample of 10 Tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

$$\%\text{Friability} = \frac{Wo-W}{Wo} * 100$$

Dissolution study:

The drug release study was carried out using paddle apparatus as per USP monograph at 37 ± 0.5 °C and 100 RPM using 900 ml of pH 7.3 buffer as a dissolution medium. 10 ml of sample was withdrawn at predetermined time intervals, filtered through a whatman filter paper, diluted suitably and analyzed spectrophotometrically at 287 nm wavelength. Equal amount of fresh dissolution medium, maintained at the same temperature was replaced immediately. Cumulative percentage drug release at different time intervals was calculated using the regression equation generated from the standard curve.

Accelerated stability Data of Carbamazepine:

Optimized batch of carbamazpine tablets were kept in sealed vials and stored at accelerated stability condition 40°C /75 % RH and 60 °C /75 % RH for two months. The sample from either batch at each temperature was taken at definite time intervals and tested for determination of drug product stability.

RESULT AND DISCUSSION

Based on trial batches C1 to C12 were formulated and tested for in process parameters and based on the in-process results and dissolution final formula to be finalize and optimize for the process parameters.

Process Optimization Results:

Different trial batches were formulated and tested for in process parameters and the final formula (C12) were taken for process optimization trials (Table 3).

Table No. 2: Formulation composition

Sr. No.	Ingredients	Quantity (mg/Tablet)											
		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
1	Carbamazepine	320						300					
2	Eudragit RS 30D	30	15	22	22	22	22	30	15	22	22	22	22
3	Triethyl citrate	3	1.5	2.2	2.2	2.2	2.2	3	1.5	2.2	2.2	2.2	2.2
4	Talc	15	7.5	11	11	11	11	15	7.5	11	11	11	11
5	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
6	Talc	30	15	22.4	22.4	22.4	22.4	30	15	22.4	22.4	22.4	22.4
7	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	HPMC P55	60	60	70	50	60	60	60	60	70	50	60	60
10	Triethyl citrate	6	6	6	6	6	6	6	6	6	6	6	6
11	Acetone	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
12	Ethanol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
	Extra Granular												
13	Carbamazepine	80						100					
14	Cellulose, Microcrystalline (PH 102)	20.25	59.25	30.65	50.65	55.65	40.65	20.25	59.25	30.65	50.65	55.65	40.65
15	Croscarmellose sodium	30	30	30	30	15	30	30	30	30	30	15	30
16	Silica colloidal anhydrous	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
17	Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
	Total	145.35	136	175	146.4	166.4	156.4	145.35	136	175	146.4	166.4	156.4

Outcome of process optimization trials:

Table No. 3: Design space for process parameters

Sr. No.	Parameter	Range challenged	Recommended design space	Remarks
1.	Spray rate	5-20	20-40	No significant difference in dissolution profile observed for batch prepared 20-40 spray rate but below 20 spray rate will fail in dissolution
		20-30		
		30-40		
2.	Product temperature	20-25	20-35	No significant difference on dissolution profile of was observed
		25-30		
		30-35		
3.	Occupancy	60%	60-30%	60% occupancy fails in dissolution whereas 30% occupancy compiles in dissolution
		30%		
4.	Blending time	5 minutes	10-20 minutes	Blend Uniformity Analysis results of all 3 time points found satisfactory.
		10 minutes		
		15 minutes		
5.	Lubrication time	3 minutes	3-7 minutes	Blend Uniformity Analysis results and dissolution profile results found satisfactory
		5 minutes		
		7 minutes		
6.	Hardness Low Optimum High	30-50	40-100 N	No significant difference in dissolution was observed for tablets with studied hardness range.
		56-76		
		70-85		
7.	Compaction force	15 KN	15-55	No significant difference in dissolution was observed for tablets with studied compaction force range.
		35 KN		
		55 KN		
8.	RPM challenge	15	15-35	No significant difference in dissolution was observed for tablets with studied RPM range.
		25		
		35		
9.	Atomization pressure	1.0	1.0-2.0	No significant difference in dissolution was observed for tablets with studied atomization pressure range
		1.5		
		2.0		

All the critical process parameters were optimized and recommended design space for the process parameters were evaluated and finalized.

Final process parameters:

Tablet No. 4: Process Optimization

S. no	Process Parameters	Optimum
1.	Effect of Spray Rate	20-30
2.	Effect of Product temperature	25-30
3.	Effect of Hardness of Tablet	40-100 N
4.	Effect of Atomization Pressure	1.5
5.	Effect of occupancy of equipment	30-40%
6.	Effect of Loss on Drying	1.5 %
7.	Effect of Blending Time	15 mins
8.	Effect of Lubrication Time	5 mins
9.	Effect of compaction force	35 KN
10.	Effect of RPM	25-30

In-Process tests:

Tablet No. 5: Results of In-Process tests

Sr. No.	Parameters	Results
1	Diameter	13.0 – 13.4 mm
2	Thickness (Height)	3.6 – 4.2 mm
3	Average mass	599mg
4	Hardness	60.00 N (50-65)
5	Disintegration Time	1 minute 20 sec.
6	Friability	0.38

Comparative dissolution study:

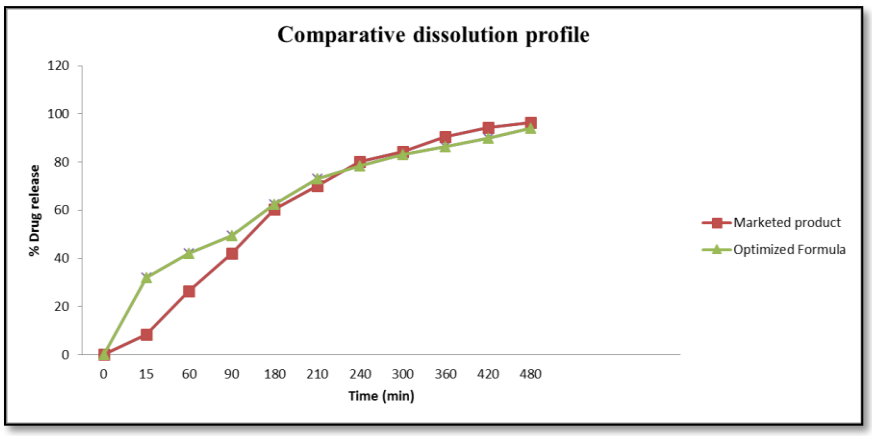

Fig. 1: Comparative dissolution of Marketed formulation Vs Final optimized formulation

CONCLUSION

Besides delivering drug to the body, a drug delivery system aim to improve patient compliance and convenience, and orally rapid disintegrating tablets are no exception. The introduction of orally rapid disintegrating dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population.

Hence, patient demand and the availability of various technologies have increased the market share of Rapid dissolving modified release tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, RDMR tablets forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular.

In the present study we have shown that RDMR tablets were highly efficient for pediatric and geriatric patient and having reduced the lag time of DR/SR dosage form.

The addition advantages of process and particle coating it provide the constant release and with this promising feature it was explored as a promising future for tablet dosage form especially in case of commercial production it was single line process with evenly coating of drug particles.

In the present study attempts were made to formulate robust, closed process, optimized, scalable formulation process parameters which were commercially acceptable with added advantages of Rapid disintegration.

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