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Chronopharmaceutical Drug Delivery of Salbutamol Sulphate for the Treatment of Nocturnal Asthma

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ABSTRACT

The objective of this study was to develop and evaluate a pulsatile drug delivery system based on drug-containing core tablet, which were coated with a swelling layer. Core tablets of Salbutamol Sulphate were prepared by direct compression using a croscarmellose sodium as disintegrant, micro crystalline cellulose as diluent and other. Core tablets were evaluated for uniformity of weight and thickness, hardness, friability, disintegration and dissolution. Compression coating over the prepared core tablets were done using various grade of HPC. Different formulae S1 to S9 were prepared using different coat % weights gain and polymer ratio. The compression forces were kept constant by adjusting constant distance between the upper and lower punches. The prepared Salbutamol Sulphate tablets were evaluated for the Lag time and in vitro release characteristics at variant pH media mimicking the gastrointestinal media. The results showed that the developed core tablets of Salbutamol Sulphate comprised excellent physical characteristics and complied with the USP criteria. For the pulsatile system, a quick releasing core was formulated in order to obtain a rapid drug release after the rupture of the polymer coating. The lag time prior to the rapid drug release phase increased with increasing % coating level.

Key word: disintegrant, swelling layer, pulsatile release tablets, compression coating, lag time.

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INTRODUCTION

Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally, chronopharmaceutical drug delivery systems should embody time-controlled and site-specific drug delivery systems[1].

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjunction with and often in response to periodic changes in environmental condition. Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Term ***Circadian*** is derived from the Latin term ***circa*** meaning “about" and ***dies*** which is derived from "a day"[2.] Asthma is a common chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. It may be classified as mild intermittent or mild, moderate, or severe persistent. Asthma affects 14 to 15 million persons in the United States. An estimated 4.8 million children have asthma, which makes it the most common chronic disease of childhood. With the increased understanding of the role inflammation plays in asthma and the addition of new pharmacologic agents, the management of this disease has improved.

NOCTURNAL ASTHMA is defined as a variable nighttime exacerbation of the underlying asthma condition associated with increase in symptoms and need for medication, increased airway responsiveness, and/or worsening of lung function. Approximately two-thirds of asthmatics suffer from nighttime symptoms. Lung function (e.g., peak expiratory flow rate or FEV1) is usually highest at 4 PM and lowest at 4 AM[3].

Pulsatile Drug Delivery System is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a pre-determined off-release period, i.e. lag time[4]

Advantages of pulsatile drug delivery:

1. Extended daytime or nighttime activity.
2. Reduced side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fever dosage units are required by the patient in therapy.

7. Drug targeting to specific sites like colon.
8. Protection of mucosa from irritating drugs.
9. Drug loss is prevented from first pass effect.

Compression coating, or press-coating, has been introduced during the period 1950-1960 to formulate incompatible drugs. This coating became interesting in the last two decades owning to the advantages over liquid coating, since the process does not need the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet[5].

MATERIAL AND METHODS

Material

Salbutamol Sulphate was obtained as a gift sample from Astron pharmaceutical Pvt. India. Croscarmellose sodium, Microcrystalline cellulose obtained as a gift sample from Maple biotech Pvt ltd. Low, medium & high substituted Hydroxy propyl cellulose (L HPC, M HPC, H HPC) obtained from Nippon soda PVT LTD Japan.

Method

Formulation of core tablets by direct compression:

The core tablets were prepared by direct compression method. An accurately weighed 4 mg of drug and other ingredients like croscarmellose Sodium, micro crystalline cellulose, aerosil and magnesium stearate were mixed by triturating in glass mortal-pestle. The blend was directly compressed at weight of 80 mg using 6 mm punch on rotary tablet machine (Rimek RSB-4 Mini press. Ltd., India.) The compositions of the formulation batches are given in **Table** 1.

Table 1: Formulation of core tablet

Ingredient	Quantity
Salbutamol Sulphate	4 mg
Croscarmellose sodium	12.5%
Micro crystalline cellulose	q.s.
Aerosil	1%
Mg stearate	2%
Total weight	80 mg

Preparation of press-coated tablets:

The core tablets were press-coated with mixed blend/granules as given in Table 1. Half the amount of Coating layer material was weighed and transferred into a 8mm die then the core tablet was placed manually at the center. The remaining coating barrier layer material was added into the die and compressed using rotary tablet machine (Rimek RSB-4 Minipress. Ltd., India.)

Factorial Design[6]

In this study, A 3^2 randomized full factorial design was used where two factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The Ratio of polymer (M HPC: L HPC) and % weight gain were selected as independent variables. Table 2 summarizes dependent and independent variables and the resulted formulations are listed in table 3.

Table 2: Experimental design: Independent Variable

Coded Factor	Level	Factor 1 Polymer ratio	Factor 2 % weight gain
-1	Low	1:1.5	125%
0	Intermediate	1:1	150%
1	High	1.5:1	175%

Tablet 3: Formulations of Factorial design batches.

Formula	M HPC : L HPC	% Weight gain
S1	1:1.5	125%
S2	1:1.5	150%
S3	1:1.5	175%
S4	1:1	125%
S5	1:1	150%
S6	1:1	175%
S7	1.5:1	125%
S8	1.5:1	150%
S9	1.5:1	175%

Evaluation of Core Tablet

Core tablets were evaluated for hardness, weight variation, friability and in vitro dissolution behavior according to standard pharmacopoeial procedures. The hardness of the tablets was determined by the Monsanto hardness tester. To calculate weight variation, 20 tablets were weighed individually and the average was calculated. Individual weight was then compared to the average weight. Weight variation was found to fall within the USP limit (± 0.5%). Friability test was carried out using 20 tablets. The tablets were pre-weighed and placed in a Roche friabilator (Electrolab, India. Model: EF 1W) operated for 100 revolutions. Tablets were then dedusted and reweighed. The difference in weights was used to calculate the friability.[7]

Evaluation of Compressed Coated Tablet

Drug-excipient interactions[8]

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. FTIR spectra were obtained by using an FTIR spectrometer~430 (Shimadzu). Prepared compressed coated formulation was taken into consideration for FTIR study. The drug Salbutamol Sulphate and Formulation previously ground and mixed thoroughly with potassium

bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders. Scans were obtained at a resolution of 4 cm-1, from 4,000 to 600 cm-1.

Rupture test (lag time) [9]

The lag time of pulsatile release tablets is defined as the time when the outer ethyl cellulose coating starts to rupture. It was determined visually by using the USP II paddle dissolution apparatus (900 ml of 0.1 N HCl, 37.5°C, 50rpm, n = 3).

Water uptake study[10]

The % water uptake of pulsatile release tablets was determined in medium filled containers placed in a horizontal shaker (100 ml of 0.1 N HCl, 3 7°C, 74 rpm, n = 3). At predetermined time points, the tablets were removed from the dissolution medium, carefully blotted with tissue paper to remove surface water, weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The %water uptake was calculated as follows:

$$\%\text{Water uptake} = \frac{Wt - W0}{W0} * 100$$

Where,

Wt is weight of wet tablet at time t and W0 is weight of dry tablet

Dissolution study[11]

The USP II rotating paddle method (37.5 ^{0}C, 100 rpm, 500 ml of 0.1 N HCl, n=3) was used to study the drug release from the pulsatile release tablets. Samples were withdrawn after predetermined time intervals and the amount of Salbutamol sulphate released was assayed with a spectrophotometer (UB Varian Cary 100 scan) at a wavelength of 277nm.

RESULTS AND DISCUSSION

Evaluation of core tablets:

Hardness and friability:

The tablets showed hardness values ranging from 4 to 5 kg/cm^2 table 4. Another measure of tablets strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In present study, the friability values for the tablet formulation were found to be <1%, indicating that the friability is within the prescribed limits.

Weight Uniformity:

The pharmacopoeial limits for deviation for tablets of more than 250 mg are ± 5%. The values are found between 306±1.89 and 323±2.93 (table 4). The average percentage deviation for all

tablet formulations was found to be within the specified limits and hence all formulations complied with the test for weight variation.

Table 4:Results of evaluation of core tablet

Sr. no.	Parameter	Results
1	Weight variation test	80 ± 3 mg
2	Uniformity of thickness	2.24 ± 0.1 mm
3	Hardness (kg/cm^2)	4.5
4	Friability (%)	0.24%
5	**Disintegration time (sec.)**	**10**

Thickness:

Tablets from all batches showed thickness values in the range of 2.7±0.3 to 3±0.5 mm (table 4).

Uniformity of drug content: [12]

Good uniformity in drug content was found within and among the different types of tablet formulations (table 4). The values ranged from 97±1.12 % to 101±1.023 % of labeled amount. Hence the tablet prepared passes the pharmacopoeial limit.

Disintegration time[13]:

As per the requirements of pulsatile tablets the core tablet should give rapid and transient release. The tablets prepared by using micro crystalline cellulose as diluents give disintegration time of 10 second (table 4), where Croscarmellose sodium was used as super disintegrant. The studies showed that the tablet hardness affects the disintegration time, harder the tablet more the disintegration time. Hardness from 4 to 5 gives best disintegration results being in its own limits.

Drug-excipient interactions

From the spectrum (**Figure**: 1), it was seen that the major peaks of drug has not changed, so this indicate there are no interactions between drug and excipients.

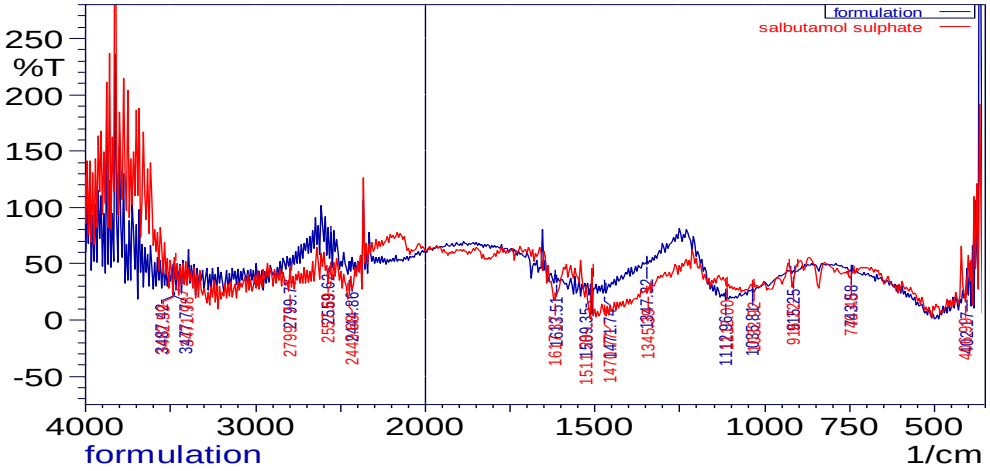

Figure 1 FTIR study of the pure drug alone and the drug combine with the excipient.

Rupture test (lag time)

Lag time of the all batch is shown in Table 5.

Table 5: Lag time of S1 to S9 batch

Batch	S1	S2	S3	S4	S5	S6	S7	S8	S9
Lag time (min)	90	195	240	120	240	330	195	370	450

Swelling index study

The swelling index of the coated tablets was attributed to fluid uptake by M HPC and L HPC content in the preparation, since M HPC and L HPC were the only components in the final compressed-coated tablets having swelling abilities. Maximum swelling index was observed for the tablets of S4, S7 and S8 in 1 hr and coating rupture at 2, 3:15 and 6:10 hr respectively. Data is given in Table 6.

Table 6:Swelling index of S1 to S9 batch

Batch	S1	S2	S3	S4	S5	S6	S7	S8	S9
% Swelling	57.89%	54.30%	49.39%	64.93%	58.71%	52.52%	66.98%	62.90%	57.31%

Table 7: Drug release study of batch S1 to S9

	% Drug Release								
Time(hrs)	S1	S2	S3	S4	S5	S6	S7	S8	S9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.00	0.00	0.00	0.91	0.00	0.00	0.00	0.00	0.00
1	1.82	1.82	1.82	1.83	0.91	1.82	1.82	0.00	0.00
1.5	1.85	1.85	1.85	1.86	0.92	1.85	1.85	0.00	0.00
2	36.42	1.88	2.79	2.80	1.85	2.79	2.79	0.00	0.00
2.5	101.11	3.44	3.45	42.53	2.29	3.45	5.69	2.23	1.12
3		3.49	4.63	99.04	3.45	3.51	63.82	2.27	1.13
3.5		57.12	4.70		3.50	4.68	100.59	2.31	2.27
4		103.83	38.26		13.60	4.76		3.46	2.31
4.5			102.51		97.53	4.83		3.52	2.34
5						71.87		3.57	3.50
5.5						105.43		4.74	3.55
6								4.82	4.72
6.5								35.03	4.80
7								99.57	4.87
7.5									14.99
8									100.06

Dissolution study

Compressed-coated formulations were subjected to preliminary in vitro release studies for a period of 8 h. Dissolution was performed in different medias, such as simulated gastric fluid (pH

1.2 acidic buffer) for the first 2 h, and simulated colonic fluid (pH 6.8 PBS) for the subsequent 7h. In the dissolution studies, the USP I apparatus was quite suitable for carrying the samples in the next medium and dissolution is continued without disturbing and touching to the surface of a coated tablet. The release profile obtained for all the batches are shown in table 7 & figure 2.

The optimized batch (S8) shows 4% drug release in 6 h. After 6 h and 10 min lag phase, there-after 35% of drug release in 6:30 h followed by 99% in 9 h. In the batch S1 and S4 there was a lag phase of less than 3 h which is not suitable for chronotherapy of asthma. In batch S2, S3, S7 and S5, there was drug release at 4 hr . The reason may be the lower the amount of M HPC as compare the L HPC. Batch S6 and S9, shows drug release between the 6 to 8 hr. The swelling property of L HPC was more than M HPC. Thus as the concentration of M HPC is increase as compare to L HPC then increase in lag time is observe as shown in figure 3. Moreover as weight gain is increase the lag time is increase shown in figure 4

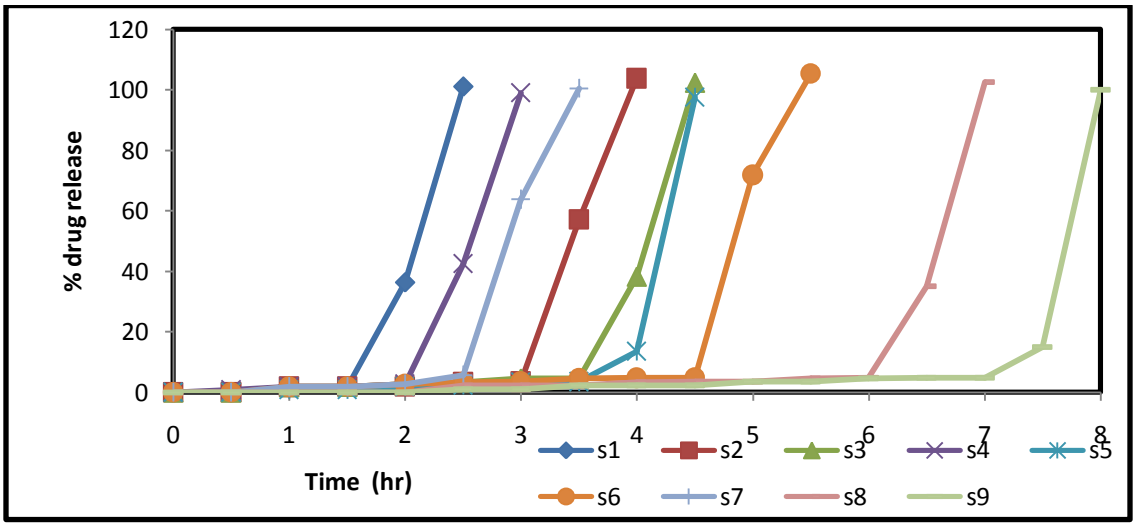

Figure 2: Dissolution profile of S1 to S9

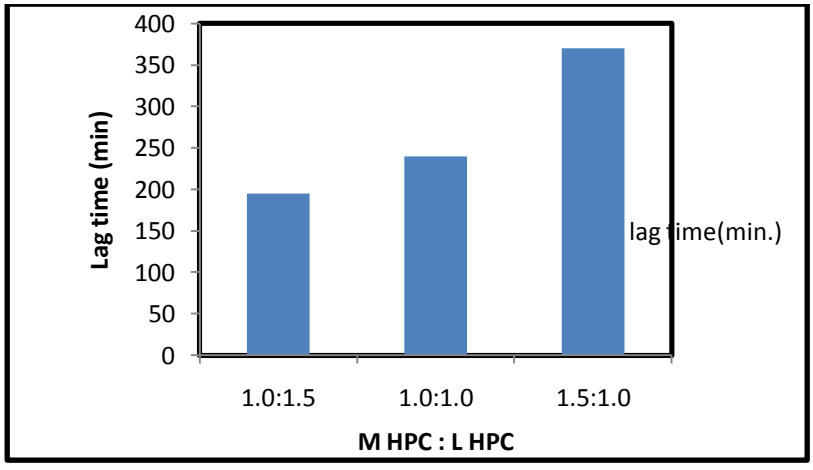

Figure 3 Graphical representation of effect of polymer ratio on lag time having constant % weight gain of 150%

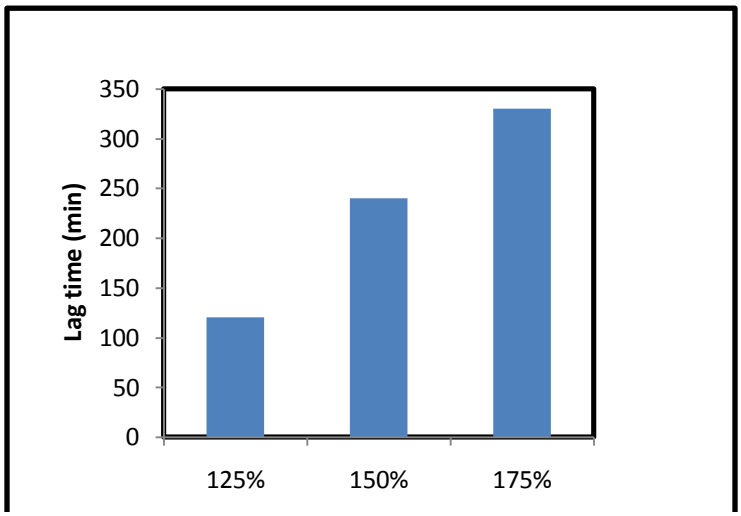

Figure 4: Graphical representation of effect of % weight gain on lag time having constant M HPC: L HPC ratio of 1:1

Dissolution Study of Optimizes Batch (S8)

Shown in figure 5

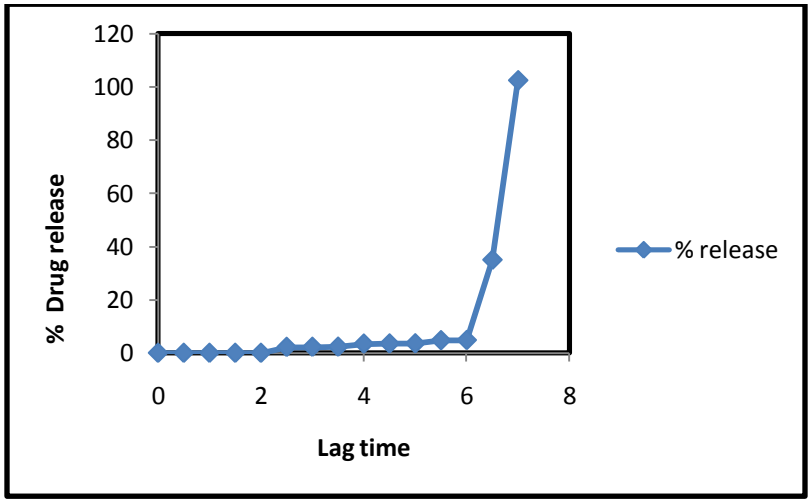

Figure 5: Dissolution profile of Optimize batch S8

Surface response plot

Figure 6 shows the lag time of pulsatile DDS using drug containing core. An X1 factor M HPC - L HPC combination, ratio, X2 factor % weight gain. The three -dimensional plot shows that the lag time of the pulsatile tablet depended primarily on the % weight gain of the polymeric layer and polmer ratio of M HPC: L HPC. With increasing % weight gain, the lag time was prolonged due to reduced water permeation rate and the increased mechanical strength of the thicker coatings. Moreover with increasing the amount of M HPC in polymeric ratio of coating material, lag time increased. M HPC have higher grade, thus having lesser swellability then L HPC.

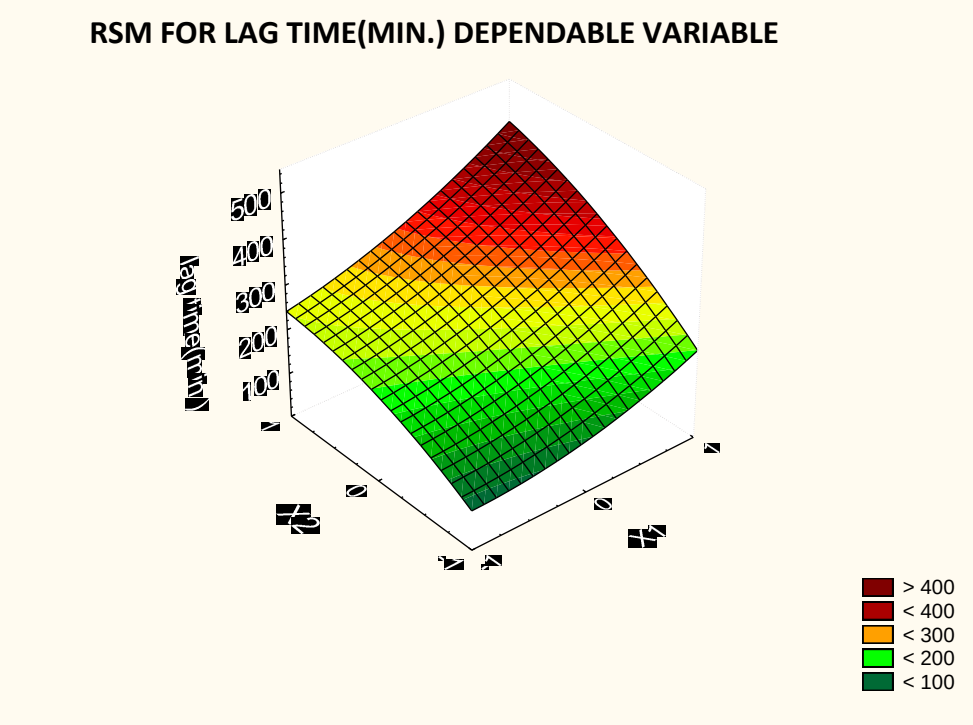

Figure 6 lag time of compressed coated pulsatile DDS with a X1 polymer ratio (M HPC: L HPC), X2 % weight gain of coating polymer.

CONCLUSION

A Coated Pulsatile Drug Delivery System for Salbutamol Sulphate to mimic the circadian rhythm of the disease by releasing the drug at appropriate time (At the time of symptoms). The system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 6 h and thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms. The release of drug was rapid and complete after the lag time. Lag time can be controlled by adjusting the percent weight gain as well as the Coating material ratio (M HPC: L HPC).

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