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Research Article

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Development and Evaluation of Process Analytical Technology (PAT) Tool For Functional Coating Weight Gain Determination By Pellet Characteristics Measurement

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Abstract: The present study is directed towards development of non-destructive Process Analytical Technology (PAT) enabled weight gain determination of functional coated pellets manufactured by Wurster coating. Currently, the traditional method of weight build up is being used wherein the complete batch is unloaded from the Wurster equipment and weighed. But this method is not accurate and do not produce exact weight gain results due to some of the reasons such as high static charges build up during unloading of pellets that make pellets to stick to wurster machine internally and hence lost during weighing, during dry loading of coating material when it is in powder form, some of it may not get loaded on the pellets and this (dry form of coating material) may get weighed during weighing of pellets (providing false weight gain results), if during initial loading small pellets are lost from the bag, then there are chances of excess weight build up because the initial input material weight has changed, etc; and if drug loaded pellets are fragile then there are chances of the drug eroding out in powder form from the pellets and drug may get coated with coating material and weighing of complete batch cannot give the exact weight gain obtained on the pellets.

Therefore, there is a need to develop PAT tools for weight gain estimation. In this work, we have successfully developed quantification techniques using DATA Count JR-PH and Gel Permeation Chromatography (Ethyl cellulose content estimation) for determining exact weight build up on drug layered pellets.

INTRODUCTION:

Wurster Coating: In 1959, the Wurster process was invented by Dr. Dale Wurster at University of Wisconsin. Since its invention all major companies are venturing into pellets coating in wurster. The process can be done with same ease for both aqueous and non-aqueous applications [1]. The Wurster process provides a high quality reproducible films and highly organised particle flow. The process parameters in the Fluid Beds are precisely controllable, which ensures easier optimization and reproducibility of the product quality [2]. This process is particularly suitable for a controlled release extended release formulation.

However, there are challenges associated with weight gain estimation in pellets system. The performance of the final modified release dosage form is greatly influenced by uniformity, thickness and morphology of the coating. For instance, if the coating is thinner than required, it will not control the release of drug for an anticipated predetermined duration which is required for sustained release. On the other hand if the coating is

thicker than required, it will result in unwanted delay in disintegration or dissolution [3,4]. Wurster coating will be used to have a strict control over the coating process in order to precisely coat the multi-particulate system.

Process Analytical Technology (PAT): PAT is defined as systems for design, analysis, and control of manufacturing processes.

Food and Drug Administration (FDA) has published several guidelines from time to time, in order to encourage pharmaceutical product development based on sound scientific rational. The objective behind the FDA's PAT guideline is to have increased understanding of product under investigation and to use the information scientifically [5]. A PAT tool greatly facilitates understanding of product Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), Critical Material Attributes (CMAs) and design space as per Quality by Design (QbD) principle [6,7]. FDA and Internation council of Harmonisation (ICH) expert working group have also published guidelines on quality systems approach to adhere with the pharmaceutical CGMP guidelines [8,9].

Data Count JR-PH: Data Count JR-PH quickly and accurately counts pharmaceutical pellets and mini tablets as small as 0.25 mm providing for the first time a much needed tool to drug developers and manufacturers that produces capsules and Tablets containing pellets. This technology can be used usually for modified release drugs in having complex dissolution profile [10]. Data Count works on the principle of light detection.

MATERIALS:

MCC Beads (ASAI KASAI, China were used as substrate for drug loading Ethyl Cellulose (Aqualon, Kentucky, US), Opadry clear YS 1R-7006 (Colorcon Inc, Harleysville, PA), Isopropyl alcohol (SD fine Mumbai, India), dichloromethane (Rankem, Mumbai, India). Materials used in the study such as API ethyl cellulose were of Pharmacopoeia standard (USP/NF). DATA Count JR-PH machine was used in pellets counting, made by Data Detection Technologies Ltd, (14 Hartom st., Har Hotzvim, Jerusalem 9777514, Israel).

METHODS:

Product selection: For method development product was selected with the formula as shown in Table 1. The desired weight gain for the coating is between 10.75% to 12.75% which is very less. If the weight gain is less than 10.75% the dissolution rate is higher and the product fails in 8 h crossing higher limits of 60%. On the other side, if the weight gain is more than 12.75%, the dissolution rate slows down at 4 h with a value less than 20%. Therefore, having exact weight gain is very important. This product was taken for challenging weight build up using Data counter technique.

Method development by DATA Count JR-PH

Selection of speed of machine: Initially, the number of pellets were first counted manually and were 1000. This pellets were subjected to different speed of machine i.e 30, 60, 100, 150, 200, and 250 rpm. Speed was finalized based on results as per Table 2.

Table 1: Batch Formula for Manufacturing of Functionally Coated Pellets

Sr.No	Ingredients	Mg/tab	Qty/Batch(Kg)
1	Drug Layered Pellets	64.75	400
2	Ethyl Cellulose 20 CPs	7.07	43.71
3	Opadry clear YSIR 7006	0.53	3.29
4	Methylene Chloride	q.s.	1216
5	IPA	q.s.	304.26

Table 2: Effect of Speed Variation on Accuracy Of Pellet Counting

	Speed	Manually Counts	Counting by machine
1	30	1000	998
2	60	1000	997
3	100	1000	990
4	150	1000	878
5	200	1000	865

Day to day to variation study: The speed for pellets counting was finalized to 60 rpm based on study results. 60 rpm speed was again challenged to study day to day variation. Manually counted 1000 number of pellets was analyzed on 5 different days to understand the variability in day to day numbers of counts. The results are discussed in Table 3 that represents not much variation

Table 3: Inter Day Variations in Pellet Counting Measurements

Sr.no.	Number of Days	Speed (RPM)	Manually Counts (numbers)	Machine Counts (numbers)
1	Day 1	60	1000	999
2	Day 2	60	1000	998
3	Day 3	60	1000	997
4	Day 4	60	1000	997
5	Day 5	60	1000	999
				Mean-998 SD-1

Average weight determination of counter pellets: Percent weight build up was done as per formula given below.

$$\%\text{Weight gain} = \left\{ \frac{\text{Average weight of coated pellets} - \text{Average weight of uncoated pellets}}{\text{Average weight of uncoated pellets}} \right\} \times 100$$

Initially five different sets of pellets were counted manually and then subjected to the data Counter machine for counts. Pellets were counted manually and divided in five different sets containing 1000 number of pellets each. Each set was weighed independently and average weight was

calculated. The average weight of these five sets is reported in the Table 4.

Table 4: Study of weight variation in manually counted 1000 number of pellets

Sr.no.	Sets	Manually count (numbers)	Machine count(numbers)	Weight(Mg)
1	Set-1	1000	996	71.45
2	Set-2	1000	992	74.11
3	Set-3	1000	997	70.98
4	Set-4	1000	996	73.21
5	Set-5	1000	998	75.45
				Mean-73.04 SD-1.85

Achieving weight uniformity: Weight variation may lead to difference in weight build up on coating, hence it was decided to sift the pellets for uniformity. The original pellets size was #30/60 ASTM passed. Difference fractions were taken and 5 set of each fraction was subjected to pellets count and weight estimation. The results are reported in Table 5.

Table 5: Particle Size Selection of Pellets To Minimize Weight Variation Fixed Number Of Pellets

Sr.no.	Sets	Manual count (numbers)	Machine count (numbers)	Weight (mg)
Sieve size #30/60 (ASTM)				
1	Set-1	1000	992	70.12
2	Set-2	1000	991	74.24
3	Set-3	1000	990	71.98
4	Set-4	1000	993	75.04
5	Set-5	1000	989	72.25
			Mean-991 SD-1.58	Mean-72.726 SD-1.95
Sieve size #30/50 (ASTM)				
6	Set-1	1000	996	72.12
7	Set-2	1000	995	74.04
8	Set-3	1000	998	72.98
9	Set-4	1000	994	73.14
10	Set-5	1000	986	71.25
			Mean-993.8 SD-4.60	Mean-72.706 SD-1.06
Sieve size #30/40 (ASTM)				
11	Set-1	1000	998	73.22
12	Set-2	1000	997	73.14
13	Set-3	1000	997	73.04
14	Set-4	1000	998	72.64
15	Set-5	1000	999	73.15
			Mean-997.8 SD-0.84	Mean-73.04 SD-0.21
Sieve size #30/35 (ASTM)				
16	Set-1	1000	997	73.12
17	Set-2	1000	998	73.24
18	Set-3	1000	996	73.54
19	Set-4	1000	998	72.84
20	Set-5	1000	999	73.25
			Mean-997.6 SD-1.02	Mean-73.20 SD-1.02

Weight gain determination: For weight gain determination the weight of 5 sets of uncoated pellets and coated pellets were estimated. Percent weight gain formula was

used as above. The pellets used for weight gain determination were #30 ASTM passed and #40 ASTM Retained with size range of 0.25-0.35 mm. Particle counting machine frequency and speed was set at 158.00 Hz and 60 rpm respectively. An example of weight gain determination for five different subsets of same sample is reported in Table 6.

Table 6: An Example of Weight Gain Determination Using Average Weight Of Coated And Uncoated Pellets

Sr.no.	Sets	Drug loaded pellets wt. (mg)	ER-I coated pellets wt. (mg)	Weight gain (%)
1	Set-1	0.073	0.081	10.71
2	Set-2	0.073	0.081	10.50
3	Set-3	0.073	0.080	9.99
4	Set-4	0.073	0.081	10.68
5	Set-5	0.073	0.081	10.38

Method verification: For the verification of method one of the commercial batches was selected. The samples of 100 g each were withdrawn after sprayed 15 kg quantity of coating solution. The samples were stored in glass vials closed with rubber corks and labelled properly. The samples were then analysed by pellets counter machine and tested for % weight build of drug layering and cellulosic material on the pellets using Gel Permeation Chromatography.

This procedure was repeated five times to test every stage sample and average reading of sample was recorded by calculating the weight of single pellet, and finding out the weight gain using weight gain formula given in above section. The results are reported in Table 7. Also, inter day variability was also determined by repeating the same procedure for 5 days.

Dissolution study of samples: Further in order to understand change in dissolution profile with respect to increase in percent weight build-up, dissolution study of all 35 samples was performed by dissolution method given below:

Medium:-Phosphate buffer, 6.8 pH
Volume:-500ml
Apparatus:-USP type-II (Paddle)
Speed:-50 rpm
Temperature:-37°C ±0.5°C
Time points:-1, 4, 8, and 20 hours.

Gel Permeation Chromatography Method Development: Ethyl Cellulose does not exhibit UV absorbance hence Gel permeation chromatography (GPC) with RI detector was selected using PLgel (300 x 7.0) mm, 5µ (Part No-PL1110-6520) for quantifying cellulose content. Tetrahydrofuran and ethyl acetate in the ratio of 50:50 were used as diluents. An injection volume of 100 µl was injected into the system at the mobile phase flow rate of 1 mL/minute for a run time of 15 minutes. Column oven temperature and detector temperature were maintained at 45°C and sample cooler temperature was maintained at 15°C.

RESULT AND DISCUSSION:

- **Selection of speed:** From Table 2, it is clear that speed of 60 rpm is giving near to accurate results when compared with manually counted 1000 number of pellets. Hence this speed is ideal for counting. Higher speeds lead to more number of pellets passing through sensor giving lesser count.

- **Day to day variation:** Based on Table 3 data it is observed that the machine gives constant results over the period of 5 days, suggesting that the speed is ideal and do not have day to day variation.

Table 7: Weight Gain Determination Of Samples Collected At Different Time Points Of Wurster Coating Study

Sr. No.	Sample Code	Theoretical weight gain achieved considering 100% efficiency	% Weight gain by Data Count JR						
			Day 1	Day 2	Day 3	Day 4	Day 5	Mean	SD
1	ER(I) 0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	ER(I) 1	0.41	0.48	0.46	0.51	0.44	0.46	0.47	0.03
3	ER(I) 2	0.83	1.10	1.16	1.21	1.18	1.17	1.16	0.04
4	ER(I) 3	1.24	1.20	1.19	1.32	1.25	1.26	1.24	0.05
5	ER(I) 4	1.66	1.32	1.31	1.36	1.33	1.34	1.33	0.02
6	ER(I) 5	2.07	1.45	1.40	1.45	1.40	1.42	1.42	0.03
7	ER(I) 6	2.49	1.61	1.58	1.60	1.62	1.65	1.61	0.03
8	ER(I) 7	2.90	1.90	1.94	1.95	1.92	1.93	1.93	0.02
9	ER(I) 8	3.32	2.29	2.31	2.31	2.30	2.33	2.31	0.01
10	ER(I) 9	3.74	2.75	2.75	2.75	2.75	2.75	2.75	0.00
11	ER(I) 10	4.15	3.00	3.01	3.05	3.11	3.06	3.05	0.04
12	ER(I) 11	4.57	3.57	3.59	3.61	3.60	3.58	3.59	0.02
13	ER(I) 12	4.98	4.18	4.23	4.23	4.19	4.20	4.21	0.02
14	ER(I) 13	5.40	4.80	4.82	4.66	4.83	4.80	4.78	0.07
15	ER(I) 14	5.81	4.88	4.95	5.05	4.99	5.01	4.98	0.06
16	ER(I) 15	6.23	5.02	5.05	5.10	5.08	5.07	5.06	0.03
17	ER(I) 16	6.65	5.50	5.55	5.58	5.56	5.57	5.55	0.03
18	ER(I) 17	7.06	5.70	5.72	5.75	5.73	5.74	5.73	0.02
19	ER(I) 18	7.48	6.11	6.15	6.18	6.14	6.12	6.14	0.03
20	ER(I) 19	7.90	6.71	6.68	6.74	6.70	6.71	6.71	0.02
21	ER(I) 20	8.31	7.21	7.24	7.25	7.23	7.25	7.24	0.02
22	ER(I) 21	8.73	7.55	7.58	7.60	7.54	7.57	7.57	0.02
23	ER(I) 22	9.15	8.00	7.98	8.05	8.01	8.05	8.02	0.03
24	ER(I) 23	9.56	8.78	8.81	8.80	8.79	8.80	8.80	0.01
25	ER(I) 24	9.98	9.05	9.06	9.11	9.10	9.09	9.08	0.03
26	ER(I) 25	10.03	9.50	9.52	9.55	9.54	9.55	9.53	0.02
27	ER(I) 26	10.40	9.30	9.31	9.33	9.35	9.31	9.32	0.02
28	ER(I) 27	10.81	10.30	10.32	10.33	10.29	10.34	10.32	0.02
29	ER(I) 28	11.23	10.71	10.75	10.75	10.73	10.72	10.73	0.02
30	ER(I) 29	11.65	11.00	11.08	11.02	11.03	11.01	11.03	0.03
31	ER(I) 30	12.07	11.08	11.10	11.11	11.09	11.12	11.10	0.02
32	ER(I) 31	12.17	11.24	11.25	11.22	11.23	11.26	11.24	0.02
33	ER(I) 32	12.59	11.90	11.88	11.91	11.92	11.90	11.90	0.01
34	ER(I) 33	13.51	12.72	12.76	12.76	12.73	12.75	12.74	0.02
35	ER(I) 34	14.42	13.00	13.01	13.01	13.05	13.03	13.02	0.02
36	ER(I) 35	15.00	14.11	14.12	14.14	14.10	14.13	14.12	0.02

- **Average weight determination of counter pellets:** The results from Table 4 shows that even though the count remains constant over the 5 different sets, there is too much of variation observed in the weight. This was attributed to the difference in the sizes of pellets leading to non-uniformities of weight. In order to decrease the variation the further trials were based on selecting appropriate size of the pellets for weight uniformities.

- **Achieving weight uniformity:** The results of the sifted pellets with difference fraction are mention in Table 5. Based on the data it was observed that

more uniform weight is observed when particle size distribution is narrow.

The fraction size of 30/40# ASTM was finalized as the weight was more uniform.

- **Weight gain determination:** Based on results from Table 6 it was reported that weight gain is uniform across batches.

Table 8: Comparison of DATA Count JR-PH result with reference analytical method of Gel Permeation Chromatography

Sr. No.	Sample Code	Theoretical weight gain achieved considering 100% efficiency	% of Cellulose gained over Drug layered pellets	% of Cellulose gained over Drug layered pellets	%Weight gain by Data Count JR Mean	%Weight gain by Data Count JR SD
1	ER(I) 0	0.00	0.00	0.00	0.00	0.00
2	ER(I) 1	0.41	0.70	0.27	0.47	0.03
3	ER(I) 2	0.83	1.32	0.14	1.16	0.04
4	ER(I) 3	1.24	1.44	0.03	1.24	0.05
5	ER(I) 4	1.66	1.39	0.20	1.33	0.02
6	ER(I) 5	2.07	1.57	0.17	1.42	0.03
7	ER(I) 6	2.49	1.79	0.04	1.61	0.03
8	ER(I) 7	2.90	2.04	0.02	1.93	0.02
9	ER(I) 8	3.32	2.46	0.03	2.31	0.01
10	ER(I) 9	3.74	2.81	0.05	2.75	0.00
11	ER(I) 10	4.15	3.18	0.17	3.05	0.04
12	ER(I) 11	4.57	3.79	0.06	3.59	0.02
13	ER(I) 12	4.98	4.35	0.10	4.21	0.02
14	ER(I) 13	5.40	4.76	0.05	4.78	0.07
15	ER(I) 14	5.81	5.21	0.29	4.98	0.06
16	ER(I) 15	6.23	5.15	0.12	5.06	0.03
17	ER(I) 16	6.65	5.70	0.37	5.55	0.03
18	ER(I) 17	7.06	5.88	0.11	5.73	0.02
19	ER(I) 18	7.48	6.34	0.05	6.14	0.03
20	ER(I) 19	7.90	6.94	0.07	6.71	0.02
21	ER(I) 20	8.31	7.45	0.14	7.24	0.02
22	ER(I) 21	8.73	7.72	0.06	7.57	0.02
23	ER(I) 22	9.15	8.19	0.23	8.02	0.03
24	ER(I) 23	9.56	8.96	0.22	8.80	0.01
25	ER(I) 24	9.98	9.25	0.21	9.08	0.03
26	ER(I) 25	10.03	9.67	0.01	9.53	0.02
27	ER(I) 26	10.40	9.48	0.29	9.32	0.02
28	ER(I) 27	10.81	10.40	0.27	10.32	0.02
29	ER(I) 28	11.23	11.00	0.22	10.73	0.02
30	ER(I) 29	11.65	11.56	0.15	11.03	0.03
31	ER(I) 30	12.07	11.70	0.31	11.10	0.02
32	ER(I) 31	12.17	11.85	0.06	11.24	0.02
33	ER(I) 32	12.59	12.11	0.03	11.90	0.01
34	ER(I) 33	13.51	12.84	0.08	12.74	0.02
35	ER(I) 34	14.42	13.10	0.17	13.02	0.02
36	ER(I) 35	15.00	14.35	0.11	14.12	0.02

- **Method verification:** Ethyl cellulose and % weight build up is mentioned in the Table 8. The result of % build up by Data Counter is in line with ethyl cellulose content. Therefore the method is good enough and is having advantage over ethyl cellulose method as it takes 15 min for weight gain estimation as

compared to 2 days of ethyl cellulose estimation. The day to day variation of weight gain for this batch reported in Table 7. Based on this data it is observed that the machine give constant results over the period of 5 days weight gain determination.

Dissolution study: Based on the results when the weight gain value of pellets by counter method is between10.75% to 12.75%, it meets required dissolution profile.

Based on the available data it was concluded that the method was capable enough to discriminate among the sample with low, high and targeted % coated pellets to get the desired dissolution profiling in the product. The results are reported in Table 9.

Table 9: Reconfirmation By Dissolution

Sr.no.	Sample Code	Weight gain by pellets counter (%)	Dissolution			
			1 hours (NMT-20%)	4 hours (20-40%)	8 hours (40-60%)	20 hours (NLT-80%)
1	ER(I) 0	0.00	70	87	90	95
2	ER(I) 1	0.47	60	79	81	92
3	ER(I) 2	1.16	55	75	80	89
4	ER(I) 3	1.24	56	73	80	88
5	ER(I) 4	1.33	56	78	80	89
6	ER(I) 5	1.42	56	74	79	90
7	ER(I) 6	1.61	56	75	79	91
8	ER(I) 7	1.93	51	74	78	88
9	ER(I) 8	2.31	52	76	80	89
10	ER(I) 9	2.75	53	75	78	88
11	ER(I) 10	3.05	50	72	77	89
12	ER(I) 11	3.59	52	74	78	90
13	ER(I) 12	4.21	46	70	79	92
14	ER(I) 13	4.78	48	72	78	88
15	ER(I) 14	4.98	44	69	75	87
16	ER(I) 15	5.06	45	70	76	87
17	ER(I) 16	5.55	42	68	78	89
18	ER(I) 17	5.73	45	70	79	90
19	ER(I) 18	6.14	41	68	75	87
20	ER(I) 19	6.71	42	70	78	86
21	ER(I) 20	7.24	40	72	80	89
22	ER(I) 21	7.57	35	70	78	88
23	ER(I) 22	8.02	33	67	78	90
24	ER(I) 23	8.80	31	66	75	87
25	ER(I) 24	9.08	29	55	64	85
26	ER(I) 25	9.53	23	45	61	87
27	ER(I) 26	9.32	21	44	64	86
28	ER(I) 27	10.32	19	45	63	87
29	ER(I) 28	10.73	19	43	67	88
30	ER(I) 29	11.03	18	45	66	89
31	ER(I) 30	11.10	17	42	62	87
32	ER(I) 31	11.24	16	42	66	88
33	ER(I) 32	11.90	15	44	62	84
34	ER(I) 33	12.74	16	42	63	85
35	ER(I) 34	13.02	14	39	55	86
36	ER(I) 35	14.12	15	35	52	88

CONCLUSION:

In this work, we accurately determined the ethyl cellulose content and percent of functional coating by using DATA Count JR-PH and we have successfully developed PAT method for analysis. The application of PAT on Extended Release coating was mainly focused on measurement of the amount of coating and coating thickness, determination of the coating endpoint and coating uniformity, mapping of the coated products, etc. Using this technique Wurster coating process can be stopped without unloading and weighing pellets.

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