A NEW APPROACH TO IMPROVE THE YIELD IN THE PRODUCTION OF SLOW RELEASE ORAL DOSAGE FORMS

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ABSTRACT

OBJECTIVE The objectives of the study were to analyse a new improved method used for the production of pellets for the manufacture of solid oral dosage forms and to compare the new method with a method previously used and studied by Bartolo in 2011.

METHOD The parameters recorded during the production of slow release pellets were collected from the Batch Manufacturing and Instructions Record (BMIR). A total of eight batches were monitored and statistically analysed, using One Way Anova, to determine whether there is a statistically significant difference between the parameters of each batch. The mean surface rating of the pallets and the yield of the active pharmaceutical ingredient (API) obtained for the monitored batches, were statistically compared to those obtained in the previous study using the Independent Sample t-test. Statistical analysis was conducted using SPSS® version 20.

KEY FINDINGS Fine tuning in the control of all parameters during the manufacturing of different batches, even within established range, improves the yield of the final product.

A statistically significant improvement in the mean pellets' surface rating (*p-value* 0.004) and percentage yield of API (*p-value* 0.030) was observed in batches analysed in this study (4.75% and 94.09% respectively) when compared to batches analysed in the previous study (3.82% and 92.43% respectively) in 2011.

The batches analysed during this study achieved the required dissolution rate after the application of the second slow release coating as opposed to the batches analysed in the earlier study, which required the application of a third slow release coating.

CONCLUSION The increase in the yield of API and improvement in the surface rating of the produced pellets implies that the new approach used for the production of slow release pellets is better and improved.

KEY WORDS Slow release, yield, surface rating, solid oral dosage forms

INTRODUCTION

Coating of solid oral dosage forms is a commonly used process in the pharmaceutical industry which has been carried out for many centuries; the first records date back to the period between the ninth and eleventh century.[2-5] The coating process was initially established to apply a sugar coating on sweets and was later adapted to be used in the pharmaceutical industry. In 1954 the coating process was further adapted to develop and introduce the application of film-coatings.[6]

Tablets and pellets are mainly coated using a fluidised bed coater or a coating pan which may either be perforated or have a solid wall. When coating pellets, a solid wall coating pan must be used since pellets may clog the perforations due to their small size.

The coating pan can be divided into two zones namely the spraying and drying zone.[5-7] In the spray zone, tablets or pellets are exposed to spray pistols from which the coating solution is sprayed.[7] One or more spray pistols may be present in a system, depending on the size of the coating pan used.[8]

The sprayed solution is pumped towards the spray nozzle by means of a peristaltic pump and on exiting the nozzle, the solution combines with air sprayed at a high pressure. This action atomises the solution into droplets.[9] This type of atomiser is known as pneumatic atomiser and is mainly used for water-based coatings to aid the drying process by inducing evaporation.[6,10] This process occurs in a fraction of a second.[6] A study using the 'Discrete Element Method' to visualise the coating process demonstrated that as the coating pan rotates, the tablets or pellets present in the spray zone appear to be almost separated, for a short period of time, from those situated outside the spraying zone.[11] During the coating process only the tablets or pellets exposed to the spray jet on the surface of the bed are coated.

The aims of this study were to determine any statistically significant difference in the parameters monitored during the production of slow release oral dosage forms of batches produced using an innovative method. Any statistically significant difference between the batches produced using the new approach and the batches produced in the previous study[1] were to be determined.

METHOD

The slow release pellets were produced using a coating pan. The coated sugar spheres, which are called pellets, were then dried using an oven. After drying, the pellets were re-introduced into the coating pan where they were coated twice with a slow release coating. The last step of the process involved the filling of hard gelatine capsules with the pellets produced.

The method used for the production of the slow release pellets in this study differed from that used previously[1] where process parameters were varied occasionally during the coating process. In this study a new approach was used. Process parameters were varied throughout the production process according to the requirements of the product. For example, over wetting, which occurred as a result of high humidity, was counteracted by increasing the temperature of the air entering the coating pan and increasing the distance between the pistols and the product bed.

The application of the API-containing coating solution onto the sugar spheres and the subsequent application of the slow release coating onto the pellets were studied. The process parameters which were of interest to this study were monitored using the BMIR.

A sample was collected from each batch and examined under a microscope, to determine the pellets' surface roughness. The surface roughness was then rated accordingly from 1 to 5 (Table 1).

Rating	Pellets' Surface Description
1	Surface is densely packed with large spikes
2	Surface is densely packed with small spikes
3	Surface has some spikes
4	Surface is irregular but no spikes
5	Surface is very smooth

Table 1: The rating and corresponding description of the Pellets' Surface Roughness

A total of eight batches of slow-release pellets were monitored. The batches chosen for this study were produced using the same coating pan used in the previous study[1] to enable comparison between the different batches. This limited the number of batches which could be analysed.

Statistical analysis was undertaken using SPSS® version 20 to determine whether there was a statistically significant difference in the parameters used during the coating process of the analysed batches. This was done using One-Way Anova test.

Following statistical analysis, parameters of the analysed batches which were found to have a statistically significant difference, were further analysed using a post-hoc test to determine which batches were different.

The yield of API and the surface roughness of the pellets after the application of the API obtained in this study were compared to the previous study[1], using the Independent Sample t-test. This analysis was performed to determine whether there is a statistically significant improvement in the yield of API using the new improved method.

RESULTS

The analysed parameters included the temperature of air entering the coating pan, temperature of the product, the pistols' distance from the product bed and pump speed, that is the speed used to pump the coating solution using a peristaltic pump.

On performing statistical analysis, it was observed that the parameters analysed during the production of the batches were all statistically significantly different from each other, except for the pistols' distance during the application phase, the product temperature during the application of the first slow release coating and the pan speed during the application of the second slow release coating.

Temperature of Air Entering	Temperature of the Product
Air Inflow	Air Outflow
Pan Pressure	Pistols' Distance
Pump Speed	Pump Flow
Pan Velocity	Pre-cooling
Air Humidity	Pan Depression
Atomisation Pressure	Film Pump Flow

Table 2: Parameters found to be statistically significant different

The surface roughness of the 28 batches produced during the study conducted previously[1] was compared to the 8 batches produced in this study. The mean surface roughness of the previous batches was 3.82[1] which is lower than that obtained for the batches analysed during this study (4.75).

Study	N	Mean	Standard Deviation	Standard Error Mean
Bartolo (2011)	28	3.82	1.335	0.252
Current	8	4.75	0.463	0.164

Table 3: Comparison of Surface Roughness

The p-value obtained for the Independent sample t-test was 0.004 which is lower than the 0.050 level of significance, implying that there is a statistically significant difference in the surface rating of the batches after coating the sugar spheres with the active ingredient.

The percentage yield of API of the 30 batches analysed during the previous study[1] was compared to the batches analysed during this study.

The mean percentage yield of API for previous batches was 92.43% which is lower than that obtained for the batches analysed during this study that is 94.09%. The resultant p-value was 0.030 which is lower than the 0.050 level of significance. This implies that the null hypothesis is rejected since there was a statistically significant difference in the percentage yield of API of the analysed samples.

Study	N	Mean	Standard Deviation	Standard Error Mean
Bartolo (2011)	30	92.43	1.920	0.350
Current	8	94.08	1.468	0.519

Table 4: Comparison of Yield of API

DISCUSSION

In the innovative method developed, parameters are adjusted, while being kept within the stipulated limits, according to the requirements of the coating process.

The pellets produced with this approach did not require the application of the third slow release coating as opposed to the batches produced during the previous study.[1] They all achieved the required dissolution rate after the application of the second slow release coating despite fine tuning of the process controlled parameters.

This shows that batches may vary from one to another due to varying conditions, such as humidity. Each batch must be treated individually and the different process parameters must be finely adjusted for the production of each batch according to the varying conditions.

When comparing the pellets' surface roughness obtained during the two studies after the application of the API, a statistically significant difference was observed. The surface of the pellets produced with the new and improved method proved to be smoother.

When comparing the yield of API obtained after the application of the API-containing solution onto the sugar spheres for both studies, a statistically significant difference was observed. The yield of API obtained for the batches produced during this study was higher.

CONCLUSION

Statistical analysis confirmed that the difference between the two set of batches is statistically significant. This implies that the method used for the production of the batches analysed during this study is better and is an improvement over the previously used method.[1]

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