Pharma Solid Knowledge Report

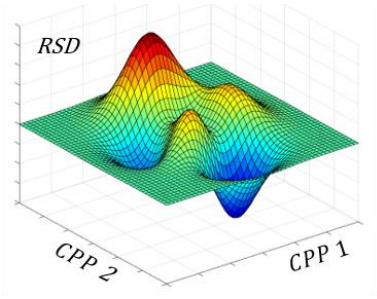
Fingolimod Gets Generic in Capsules!
Different Excipients – Different Process Parameters

A STUDY ON EXCIPIENTS TO PROVIDE AN EXPERIMENTAL DATABASE FOR FORMULATION DEVELOPMENT AND PROCESS OPTIMIZATION

For pharmaceutical formulation development, a vast number of excipients are available. Therefore, it is not surprising, that different manufacturers develop different formulations even if they are challenged with the same kind of API. For sure, the target is the same: the development of a high quality capsule product. But, which excipient delivers the best results and leads to the best product? To compare the different excipients, the capsule filling process also has to be taken into consideration.

AUTOMATED PROCESS DEVELOPMENT AT PHARMASERVICE WAIBLINGEN

Process understanding is the key when it comes to process development, optimization or validation. It is essential for this study where different types of excipients are compared. An excipient reveals its qualities only when it is handled with the correct process parameters. To find these parameters a solid process understanding is needed. With the help of the automated process development at Bosch, we are able to determine the optimal setting of the critical process parameters for each product (see knowledge report “Automated Process Development”). Our patented, automated capsule filler allows the fast and efficient execution of experiments. The experiments are mandatory to investigate the process, especially to determine possible interactions. Overall, within this study we investigated twelve different excipients regarding their performance to produce generic Fingolimod. Seven types of mannitol, four types of calcium lactate and one calcium phosphate were tested. The target fill weight was 50 mg. All tested excipients were mixed with 0.5 % magnesium stearate.



Automated Process Development (APD) for gelatin capsule fillers

Executed on Bosch patented GKF Setup

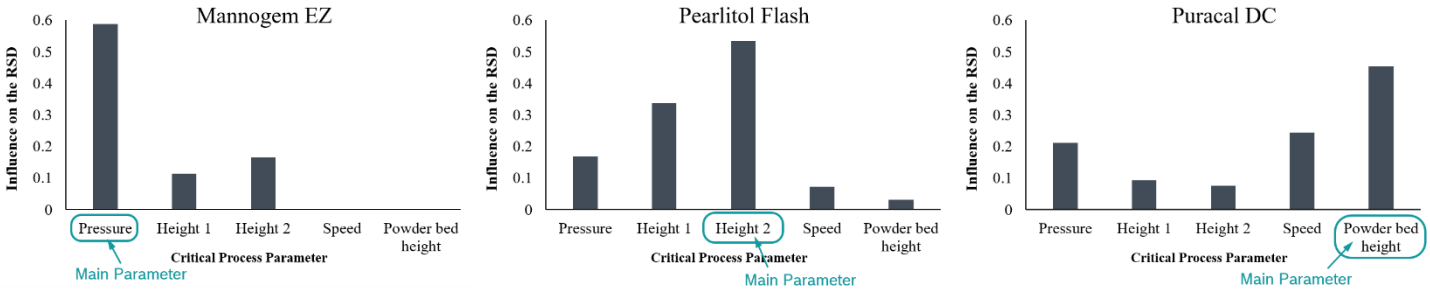
Excipient	Type	Speed (rpm)	Pressure (MPa)	Powder bed (mm)	Height 1 (mm)	Height 2 (mm)	RSD (%)
Pearlitol® Flash	Mannitol 1	120	0.08	3.1	5.0	3.1	1.1
Pearlitol® 50C	Mannitol 2	120	0.18	14.8	3.2	3.0	1.2
Pearlitol® 160C	Mannitol 3	121	0.21	15.0	3.2	5.0	1.3
Pearlitol® 200SD	Mannitol 4	96	0.08	3.0	1.0	1.8	1.3
Mannogem EZ	Mannitol 5	129	0.08	14.5	1.0	2.8	1.5
Mannogem 2080	Mannitol 6	136	0.08	3.0	1.0	3.1	1.6
Parteck M200	Mannitol 7	80	0.50	15.0	5.0	1.0	1.5
Puracal® Xpress	Calcium lactate 1	120	0.35	15.0	5.0	3.2	0.7
Puracal® DC	Calcium lactate 2	140	0.50	13.9	1.0	5.0	1.5
Puracal® PP	Calcium lactate 3	120	0.17	15.0	5.0	2.3	1.4
Calcium lactate pentahydrate	Calcium lactate 4	127	0.35	15.0	3.1	1.0	1.3
Dicalcium phosphate	Calcium phosphate 1	140	0.08	4.2	1.0	3.3	1.7

Process parameter setting: low middle high

RESULTS AND DISCUSSION

Finally, for each excipient a process model was generated. Each process model was validated by comparing predictions with subsequently executed runs. All validation runs were within the predicted confidence intervals (confidence level of 95 %). Thus, it was ensured that the models provide a valid prediction. An optimization algorithm then calculated process parameters, which lead to a minimal weight variation (relative standard deviation, RSD). The table above illustrates the optimal settings of the process parameters. Each type of setting is additionally dyed according to the calculated value. A green color illustrates a low value, white a middle level and high parameter settings are dyed blue. E.g., for Parteck M200 a middle capsule filler speed was calculated (white). Thus it is beneficial to reduce the speed to around 80 rpm (possible range 50 – 145 rpm). In contrast to this, a high speed was chosen for Mannogem 2080. With the help of the colored table, it is obvious that for each excipient a different process parameter setting is beneficial. Even within the same type of material (e.g. mannitol) the process parameters are not the same. Different mannitol needs special process parameters and it cannot be said that e.g., a high speed is in general an optimal setting for mannitol. The parameters have to match each excipient.

Pharma Solid Knowledge Report – Automated Process Development



Beside the optimal setting of the process parameters the process models can deliver considerably more information. One example is the analysis of the influences. It provides additional information to determine whether a process parameter is critical or not. The figures above show the influences of the critical process parameters for three of the twelve products. In general, the influences describe how much of the variation in the dataset is explained by each process parameter. The design of the experiments (DoE) alters the process parameters in order to determine effects and interactions. As a result, the output (i.e., the capsule weight) shows different variations. If an altered process parameter causes a high variation it has consequently a great influence on the process and is likely a critical process parameter. Obviously the influences are very different among the three illustrated excipients. For Mannogem EZ the pressure has a massive influence, for Pearlitol Flash height 2 is important and for Puracal DC it is the powder bed height.

CONCLUSION

This study illuminates again the opportunities that a good process understanding can provide. Finally, all of the investigated excipients were capable of producing a low RSD on the GKF (all below 2 %). Prerequisite was a precise adjustment of the process parameters. Therefore it is quite reasonable that e.g., the FDA demands the enhancement of Quality by Design for pharmaceutical processes. When the critical process parameters are known and the right settings are chosen, a robust and high quality process is delivered. Choosing the right settings is essential, especially when a range of excipients with different material attributes should be equally tested and compared.

The rapid automated process development is a fast and efficient approach to reach the goals of QbD. The combination of automation technology, our process knowledge and neat statistical optimized planned experiments (DoE) provides an effective way to improve, optimize, and primarily understand the overall process.

PLEASE CONTACT US

Our team "Engineering Pharmaceutical Service" will be available with all our experience of over 50 years.

Dr. Thomas Brinz
Head of Department Engineering Pharmaceutical Service
Phone: +49(711)811-58001
Thomas.Brinz@bosch.com

Robert Bosch Packaging
Technology GmbH
Stuttgarter Straße 130
71332 Waiblingen
Germany

packaging@bosch.com
www.boschpackaging.com