Additional file 1

Superstructure-based process synthesis and economic assessment under uncertainty for solid drug product manufacturing

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# Supporting Information

## Calculation of the number of alternatives in a superstructure

The alternatives in a superstructure can be calculated by the following three steps.

### Step 1: excluding special processes

The processes including unit $U\_{6}$ can be excluded from the superstructure because they are special compared with other processes. The two excluded processes are shown in Fig. S.1.



**Fig. S.1 Excluded processes in Step 1**

### Step 2: splitting into parts

The superstructure after excluding the special processes is shown in Fig. S.2. The ports that can be split are specified in Step 2 based on the streams, e.g., port 13 cannot be split because there is a stream from port 8 to 14. Consequently, six parts were obtained, as shown in Fig. S.3.



**Fig. S.2 A superstructure excluding special processes**



**Fig. S.3 Parts of the superstructure after Step 2**

### Step 3: calculating numbers

The total number of alternatives, $N\_{alternative}^{total}$ [–], can be calculated as shown in Eq. (S.1):

|  |  |
| --- | --- |
| $N\_{alternative}^{total}=N\_{alternative}^{exception}+\prod\_{part}^{}N\_{alternative}^{part}$, | (S.1) |

where $N\_{alternative}^{exception}$ and $N\_{alternative}^{part}$ represent the number of alternatives of the excluded processes and those of $part$, respectively. The calculation of $N\_{alternative}^{part}$ can also be done by repeating the steps described above. For part 1, for example, the stream from $S\_{a}$ to port 8 can be excluded as a special process, and port 1 can be split as well. The number of alternatives from $S\_{a}$ to port 1, and from port 1 to port 8 are 1 and 2, respectively. Then, $N\_{alternative}^{1}$ becomes 3 ($=1+1∙2$). Table S.1 summarizes the values of parameters. By applying Table S.1 to Eq. (S.1), $N\_{alternative}^{total}$ was calculated as 9452.

**Table S.1 Values of parameters**

|  |  |
| --- | --- |
| Parameter | Value |
| $$N\_{alternative}^{exception}$$ | 2 |
| $$N\_{alternative}^{1}$$ | 3 |
| $$N\_{alternative}^{2}$$ | 6 |
| $$N\_{alternative}^{3}$$ | 15 |
| $$N\_{alternative}^{4}$$ | 5 |
| $$N\_{alternative}^{5}$$ | 7 |
| $$N\_{alternative}^{6}$$ | 1 |

Table S.2 shows the breakdown of process alternatives in the superstructure.

**Table S.2 Breakdown of the investigated process alternatives**

|  |  |  |  |
| --- | --- | --- | --- |
| Technology | Number | Dosage form | Number |
| Batch | 8191 | Tablets | 6750 |
| Continuous | 1261 |  | *Wet granulation* | *5400* |
| Total | 9452 |  | *Dry granulation* | *900* |
|  |  |  | *Direct compression* | *450* |
|  |  | Capsules | 1352 |
|  |  | Granules | 1260 |
|  |  | Powders | 90 |
|  |  | Total | 9452 |

## Details about the case study

The detailed results of sensitivity analysis for the top 20 highest sensitive parameters are summarized in Figs. S.4 and S.5.



**Fig. S.4 Results of sensitivity analysis in Scenario 1**



**Fig. S.5 Results of sensitivity analysis in Scenario 2**

## Contents of “SoliDecision”



**Fig. S.6 Data input tab for clinical development**



**Fig. S.7 Data input tab for commercial production**



**Fig. S.8 Data input tab for product demand**



**Fig. S.9 Result tab showing the best alternative for Scenario 1**