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PHARMACEUTICAL TECHNOLOGY

OPTIMIZING FLOW AND SEGREGATION PROPERTIES OF LACTOSE/MICROCRYSTALLINE CELLULOSE MIXTURE FOR TABLET COMPRESSION

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Abstract
The present study deals with optimizing the flow and segregation properties of levocetirizine hydrochloride formulation, where the delay between homogenization and tablet compression was found to affect the tablet content uniformity. In addition to API, the base formulation comprised spray dried lactose monohydrate, milled lactose monohydrate 200 mesh, Avicel PH 101 microcrystalline cellulose, and minor excipients. Several alternative mixtures were prepared using the same total composition, but different grades of lactose and microcrystalline cellulose. These mixtures were then tested for the segregation behavior in an in-house segregation device and the flow properties using the Freeman FT4 powder rheometer. The segregation tests showed the grade of lactose is essential for mixture in-flow segregation. While SD lactose mixtures increased the API content in a direction countercurrent to flow, the milled lactose mixtures segregated API concurrently. Mixtures using both lactose grades showed combined effect, resulting in the least segregation due to the two segregation processes competing with each other. However, the segregation was extremely sensitive to ageing of the mixture. It was also found that each type of lactose causes a different flow regime of the mixture in process vessels. In order to improve the content uniformity of the tablets, it was found the volumetric flow regime of transport to tablet press is required as well as the aggregate formation should be prevented.

Introduction
Lactose monohydrate/microcrystalline cellulose mixtures represent widely used formulation base for direct tablet compression. Both the lactose and celluloses are available in many grades, allowing for optimizing the flow and segregation properties of the formulation. The flow and segregation behavior may become even more complex, if other components of the mixture exhibit time-sensitive flow characteristics.
The present study deals with optimizing the flow and segregation properties of levocetirizine hydrochloride formulation based on lactose/microcrystalline cellulose mixture for direct tablet compression. During the process validation, an interesting behavior was observed. Namely, if there was a delay between the homogenization and the tablet compression, the duration of the delay affected the resulting tablet content uniformity. Since the mixture homogeneity was good and constant after the mixing step, the transport of the mixture to tablet press during the batch processing was suspected to be the critical step. The aim of this study was therefore to investigate mixture flow from the homogenization container to the tablet press inlet as well as the ability of the mixture to segregate during the gravitational flow. The study objective was to determine the sensitivity of the aspects above to the mixture composition, the component properties, and the time delay between unit operations.

Experimental
The experimental part of the study involved designing suitable model formulations, their preparation and subjecting the samples to segregation and flowability tests.

Mixture composition and preparation
The base formulation comprised levocetirizine hydrochloride (5 % w/w), Flowlac 100 spray dried lactose monohydrate (52.5 %), milled lactose monohydrate 200 mesh (15 %), Avicel PH 101 microcrystalline cellulose (MCC, 25 %), sodium starch glycolate (1 %), colloidal silicon dioxide (Aerosil 0.5 %) and magnesium stearate (1 %). Several alternative mixtures have been prepared with the same total composition, but using different proportions of different types of lactose and microcrystalline cellulose. The composition of prepared mixtures

is summarized in Table I. The preparation procedure involved introducing all ingredients except the magnesium stearate into the vessel of tote blender 0.8 l, through a 1 mm screen, blending for 20 minutes at 28 rpm, then adding magnesium stearate and additional blending for 5 minutes.

Table I
Composition of model formulations involved in the case study

Component	API	Lactose 200 M	Lactose SD	MCC	Other
Sample ID	wt. %	wt. %	wt. %	wt. %	wt. %
SMix	5	15	52.5	25	2.5
SLacSD	5	-	67.5	25	2.5
SLac200	5	67.5	-	25	2.5

Segregation tests

The segregation behavior of prepared mixtures was carried out in an in-house segregation device. The device consisted of two glass tubes (250 x 25 mm) equipped by a connector, enabling the powder to flow from one tube to another and taking samples during the process. The operation of the segregation device was as indicated in Fig. 1. The mixture to be tested was placed into the upper tube and the connector was opened, so as to allow the powder to flow gravitationally from the upper cell into the bottom cell. After the transfer was completed, the tubes switched their position and next cycle of the test was started. The test was finished after 30 cycles. The samples of the mixture were taken during cycles no 1, 5, 10, 15, and 30. The sampling cycles involved taking five samples per cycle during the powder flow from one tube to another. The position of the sample taken was recorded. The samples were then analyzed using HPLC, so as to determine API content.

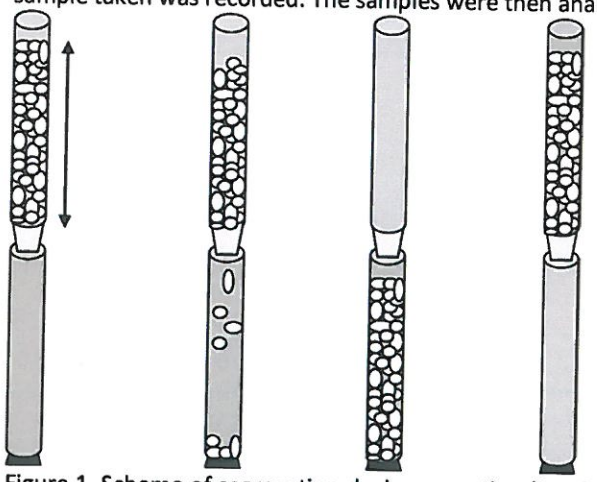

Figure 1. Scheme of segregation device operation (1. mixture is placed into the top cell; 2. mixture is flowed to the bottom cell, samples are taken during the process; 3. finished flow cycle; 4. the top and the bottom cells are swapped and next cycle begins)

Flow properties

The powder rheometry was used to analyze powder flow characteristics of the sample mixtures using the Freeman FT4 powder rheometer. The test set included measuring the flow energy in both the forced flow and the unconfined flow regime. The stability of flow properties of the samples exposed to test conditions was also measured at the forced flow conditions. Shear tests were also performed in order to determine the internal friction and wall friction parameters. Wall friction experiments used the Ra ≤ 0.05 μm stainless steel standard as an approximation of wall material of the process equipment.

Results and Discussion

The primary focus was on API and major excipients used throughout this study. Since the use of minor excipients (sodium starch glycolate, Aerosil, and magnesium stearate) was unavoidable and their proportion in the mixture had not to be changed, their effect on the mixture behavior was not examined thoroughly. The assumption was that although their effect may be significant, it will not change significantly over the alternative formulations included in the comparison. The key components particles were examined for their morphology and particle size distribution using SEM (Fig. 2) and laser diffraction (Tab. II). The API particles are smallest of all key components by large margin and the Fig. 2 shows significant tendency of the material to aggregate. Lactose

200 M and MCC are of medium particle size, with the lactose having significant portion of fines. Particles of lactose SD are the largest, spherical, but formed as agglomerates of smaller crystals. Owing to these facts, the API will obviously form interactive mixtures at least partially with some of the excipients, which may affect the segregation behavior of the formulation.

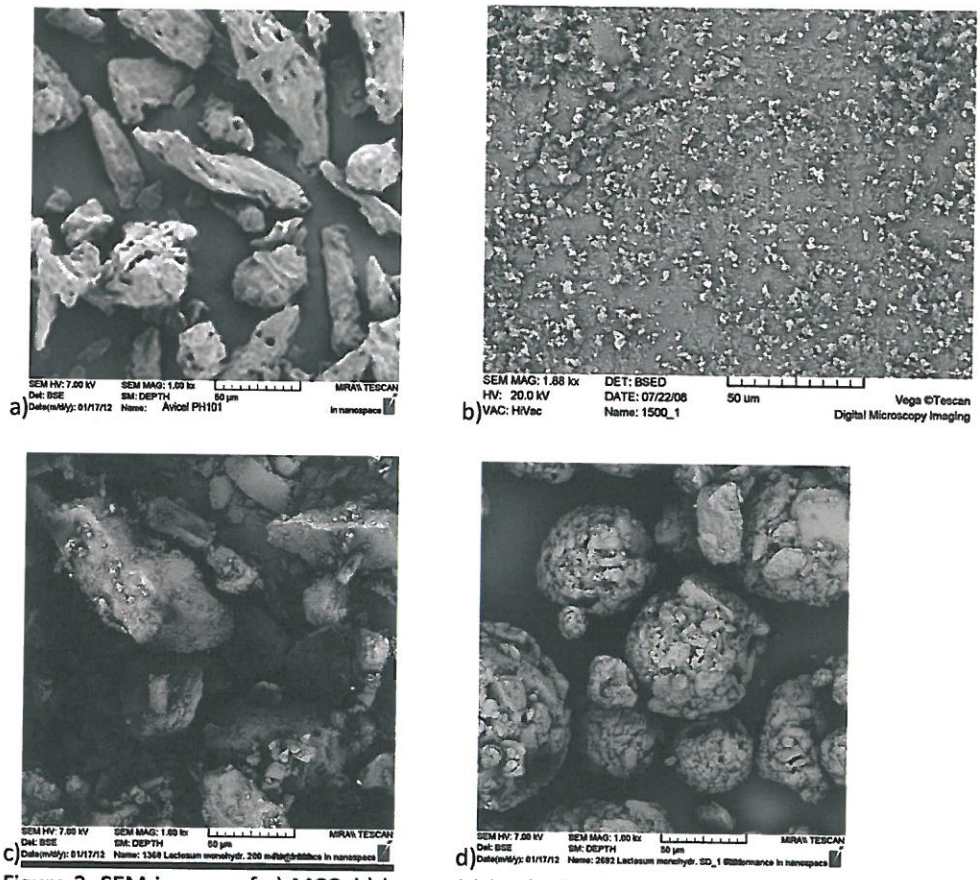

Figure 2. SEM images of a) MCC, b) levocetirizine hydrochloride, c) lactose monohydrate 200 mesh, d) lactose monohydrate SD

Table II

Particle size distribution of key components of model formulations (Malvern Mastersizer 2000)

	PSD, µm			
	API	Lactose 200 mesh	Lactose SD	MCC
d(0,1)	0,2	5	30	30
d(0,5)	5,7	30	120	50
d(0,9)	19,0	100	250	85

Segregation tests

All prepared formulations were tested for their tendency to segregate. Powder mixtures may generally segregate by several mechanisms, but during the gravitational flow, the 'sifting' and 'fluidization' are the most important ones. The term sifting means percolation of finer particles through the voids between more coarse particles, leading to fines being accumulated downstream the powder flow direction. The fluidization may lead to finer particles being slowed down more than coarse ones due to the aerodynamic resistance, and hence they accumulate upstream the powder flow direction. Using the segregation device described above, the 30 cycles of the segregation test were carried out for each formulation. Illustrative results for SMix formulation are provided in Fig. (a-e). In each sampling cycle, five samples were taken along the segregation tube and the API content was determined using HPLC. Figure shows, that the concentration of API is not constant, but increases in the upwards direction of the segregation tube, after the first cycle. This trend becomes more pronounced in further sampling cycles. So as to obtain single-number overall measure of segregation the profiles are approximated by linear regression. The slopes of regression profiles (K) were plotted vs the

sampling cycle number and again processed by linear regression to provide segregation index KK. Although the linear approximation may not seem justified in some cases, it provides good overall trend indicator. The segregation index value is a good measure of the mixture tendency to segregate and positive or negative value may indicate the general direction of segregation trend.

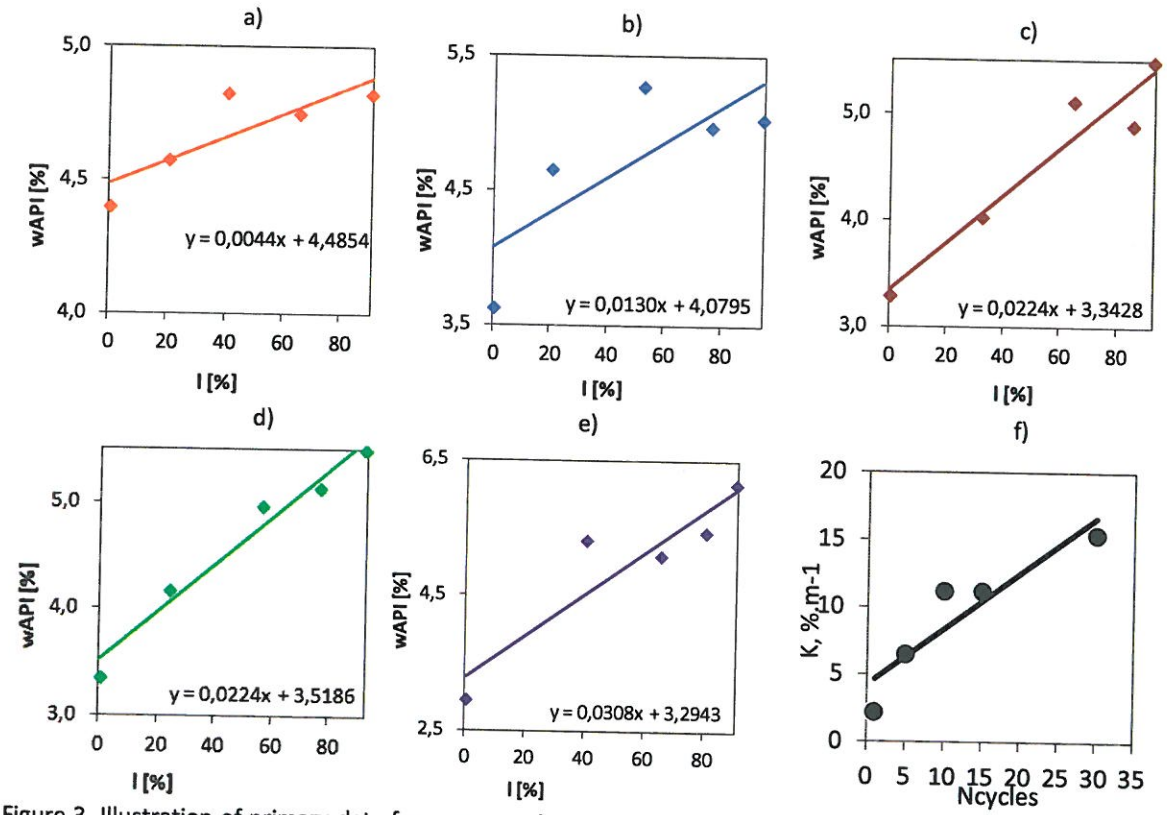

Figure 3. Illustration of primary data from segregation test obtained for SMix formulation after 1 (a), 5 (b), 10 (c), 15 (d) and 30 (e) test cycles. The tube length starts at 0 % at its bottom. The slopes K of profiles a-e are plotted vs the number of test cycles (f)

Table III
Segregation indices of model formulation

KK, $\%.m^{-1}.\{ncycles\}^{-1}$			
SMix (I)	SMix (II)	SLac200	SLacSD
0.415	−0.400	−3.795	2.475

Results of the segregation tests are summarized in the Table III. Formulation SMix was prepared in two batches (I) and (II) which were both tested independently. The results revealed, there are multiple segregation mechanisms taking part in the overall segregation behavior. SLacSD mixture exhibits large positive segregation index. The positive value means the API tends to accumulate at the upper side of the segregation device tube, i.e. it accumulates upstream the flow direction. The API has the smallest particle size in the mixture; hence the segregation due to fluidization is the dominant mechanism in this case. Surprisingly, there is neither evidence of interactive mixture formation, nor any effect of it affecting the segregation, despite the SD lactose particle textured surface. Most likely, the surface area capacity of relatively big SD lactose particles is not large enough to bind significant portion of API. SLac200 mixture exhibits even larger, but negative segregation index, meaning the API accumulates downstream the powder flow during the segregation test. It may suggest there is sifting segregation acting in place, but it may hardly be the only process responsible for it. API-lactose aggregates are likely responsible for the part of the observed effect. The lactose 200 mesh is much more cohesive and the aggregates are able to develop, encapsulating the API. Those aggregates are bigger than any other primary particles present and they would segregate downstream by the fluidization mechanism.
Both batches of SMix formulation exhibit low segregation index value due to balanced effects of two opposing segregation effects demonstrated above. However, there is quite substantial difference between the results of

the two batches, which means the balance is rather sensitive to batch-to-batch variability. Thus, the SMix formulation is resistant to segregation at its nominal quality, but problems may arise, if the mixture properties change during the manufacturing process. One of the important properties, that may be easily changed during the process or process delay are the flow properties and resulting flow regime of the mixture from the blender contained into the inlet of the tablet compression machine. Therefore, it was very important to examine the flow properties of the formulations.

Flow characteristics of the test formulations

Flow properties were measured at both forced flow conditions and the unconfined flow conditions. Stability test was performed at forced flow conditions at 100 mm/s tip speed of the blade (Fig 4a). The results indicate the mixtures containing SD Lactose may exhibit significant change of properties during the flowability tests. It also means the material property may change during time, if the material experience prolonged exposition to high-stress conditions. There is substantial difference between SMix I and II batches at the beginning, but the curves approaches each other. It indicates the SMix I probably suffered more mechanical damage during preparation and processing and thus it has the properties similar to those SMix II is getting to have after six repetitions of the stability test. It is not clear what the cause of this difference is, but the important conclusion is that the mixtures are rather unstable. The comparison of absolute values of total energies shows the SLac200 mixture possesses the smoothest particles and hence the lowest energy is required for flow at high-stress conditions. Such conditions are not much relevant to container-tablet press transport though and the situation in variable tip speed test was entirely different. The total energy consumption increases for SLac200 substantially as the tip slows down due to bigger and bigger "cake" of the powder is carried by the blade, suggesting the mixture is cohesive. This is important finding, as it supports assumption of aggregate formation in SLac200, which are supposed to be responsible for the negative segregation index observed. The cohesiveness of the SLac200 mixture is verified also by the higher value of specific energy for unconfined flow, compared to other formulations (Table IV).

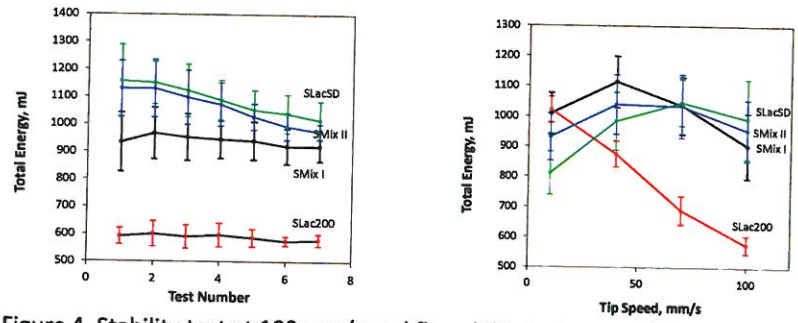

Figure 4. Stability test at 100 mm/s and flowability test at variable tip speed measured in FT4

Table IV

Powder properties for test formulations measured using FT4 powder rheometer

Formulation/Parameter	SMix	SLacSD	SLac200
Total energy at forced flow, mJ	954	971	588
Specific energy at unconfined flow, mJ/g	5.8	5.1	6.5
Wall-friction angle, δ°	8.0	7.0	7.2
Eff. Internal friction angle, ϕ_e°	30.1	30.5	37.1

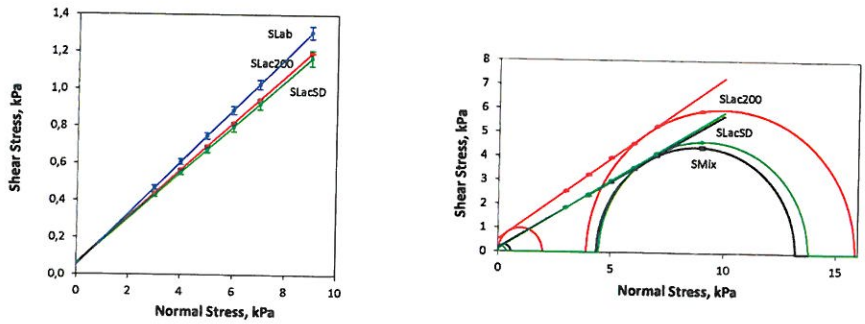

Figure 5. Wall friction test (Ra = 0.05 um) and shear test at 9 kPa pre-shear measured in FT4

Because of the substantial differences among the flow properties of the different mixtures, the flow regime of the mixture for tablet compression being discharged from the blender container to be brought into the tablet press, may be different. In pharma industry, the mass flow is generally preferred, as it is gentler to the particles due to low inter-particle shear, as well as it exhibits reduced relative movement of particles and hence less opportunity for the segregation to proceed. In order to find out, which flow regime is to be expected, the Jenike procedure was applied. The procedure requires three parameters of the flowing powder to be determined. First, the slope of the container wall was 45°. Second, the wall friction angle was determined by wall friction test using the polished steel wall sample (Ra = 0.05 um roughness). The values are very similar for all three formulations (Fig. 5, Table IV). Third, the effective angle of internal friction was found being higher for SLac200 mixture, than for any other mixture.

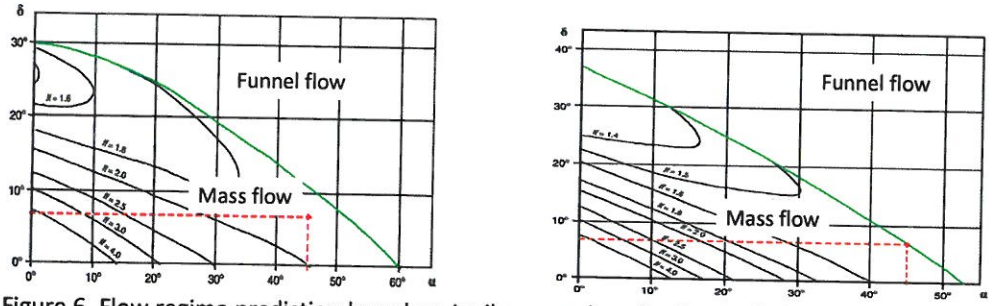

Figure 6. Flow regime prediction based on Jenike procedure for SLacSD (left, ϕ_e = 30°) and SLac200 (right, ϕ_e = 40°). Diagrams taken from[3].

Fig. 6 shows the graphical representation of Jenike design procedure. While the SLacSD formulation is expected to flow safely in the mass flow regime, the SLac200 is expected to exhibit transient behavior, as the flow parameters are at the boundary between the mass-flow and funnel-flow regions. The same is true in limited extent for the SMix formulation. The formulation is expected to flow in a mass flow regime, but relatively slight change in properties or process parameters can shift the flow patterns into the funnel flow regime.

Conclusions

The segregation tests showed the grade of lactose used is essential for mixture segregation during its flow. While SD lactose mixtures increased the API content in a direction countercurrent to flow, milled lactose mixtures promoted the API segregation concurrently to flow. Mixtures using both lactose grades showed combined effect, resulting in the least segregation due to the two segregation processes competing with each other. However, the segregation was extremely sensitive to ageing of the mixture due to formation of aggregates. The aggregates form and disintegrate during mechanical processing and cause non-uniformity of the tablet content. It was also found that each type of lactose used, causes a different flow regime of the mixture. In order to improve the content uniformity of the tablets, it is needed to ensure the volumetric flow regime in the hopper (by using specific type of lactose), or to ensure that tablets pressing follows the homogenization as soon as possible in order to minimize the time for aggregate formation. In order to improve the content uniformity of the tablets, it was found the volumetric flow regime of transport to tablet press is required as well as the aggregate formation should be prevented. This objective can be achieved by minimizing the delay between mixing and compression, but the more robust way would be e.g. dry-granulating the API premix.

Acknowledgment

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