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IMPACT OF TOOLING SIZE ON THE HECKEL PROFILE AND DERIVED COMPRESSIBILITY PARAMETERS

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PURPOSE

First-in-human (FIH) studies represent a fundamental milestone during drug development of new chemical entities, with primary objective to establish as soon as possible pharmacokinetic profile, safety and tolerability in order to reduce the risk of moving to Phase II candidate with significant risk of failure [1].

To grant quick access to FIH studies the simplest combinations of dosage form, composition and production process fitting the study purpose are commonly used. However, there are reasons to use robust formulations and processes from the early clinical development, raising the challenge of developing as quickly as possible blends suitable for production of capsule or tablets on automatic intermediate-high speed equipment.

The development of a tablet is very challenging during early clinical phases because of dose uncertainty, limited active pharmaceutical ingredient availability and short lead times [1].

Compressibility assessment provides fundamental information for the selection of excipients combination with active ingredient to obtain a blend suitable for tablets formation. Determination of compressibility profile with small scale experiments could allow to significantly reduce the amount of active ingredient required for the formulation screening of a blend to be directly compressed into tablets.

This work aimed to establish a general pre-formulation screening method based on generation of compressibility data for active ingredient using punches as small as possible. For this reason, compressibility of four active ingredients was assessed using round punches of 11.28 mm and 5.64 mm diameter, looking for comparability. In case the smallest tooling could be used, the amount of drug required for a compressibility study is reduced by 75%.

METHODS

Active ingredients selected for this work were: niacin (Lonza AG, CH), ibuprofen (BTC Europe GmbH, D), NCE1 and NCE2 (two Evotec new chemical entities).

True density (AccuPyc II 1345 pycnometer, Micromeritics, USA), particle size distribution (Helos KF, Sympatec GmbH, Germania) and surface area (TriStar II 3020 Micromeritics, USA) were measured for all the active ingredients.

Compressibility test was conducted using instrumented single punch tablet press (EK0, Korsch AG, D), applying the out of die approach, considered the most suitable because based on tablets thickness after ejection, a condition more representative of the actual tablets properties.

The tablet press was fitted with round flat faced tooling; the powder aliquots were weighed and loaded manually into the die, then compression was applied at the target pressure. For each target pressure five compacts have been prepared.

Details of the conditions applied according to the experimental plan are presented in Table 1.

All the compacts obtained have been characterized for weight (analytical balance Sartorius Secura 224i-1s) and thickness (digital caliper 0.01 mm, Mitutoyo Ltd, J) just after production and after 24 hours of storage in double polyethylene bag at controlled room temperature and moisture (20-25°C, 50-65% RH).

Bulk density, solid fraction and porosity values were derived from the measured properties of active ingredients and compacts [2-4].

Heckel (HK) equation was used to fit experimental data and obtain mean yield pressure (Py), widely used indicator of powder compressibility [2-4].

		Compression Force (KN) to obtain selected target pressure					
Tooling diameter (mm)	Test powder weight (mg)	30 MPa	90 MPa	140 MPa	200 MPa	240 MPa	300 MPa
5.64	100	0.75	2.25	3.50	5.00	6.00	7.50
11.28	400	3.00	9.00	14.0	20.0	24.0	30.0
22.00	1600	11.4	34.2	53.2	NA*	NA*	NA*

Table1 - Conditions applied in compressibility experiments with tooling of different diameter.

RESULTS

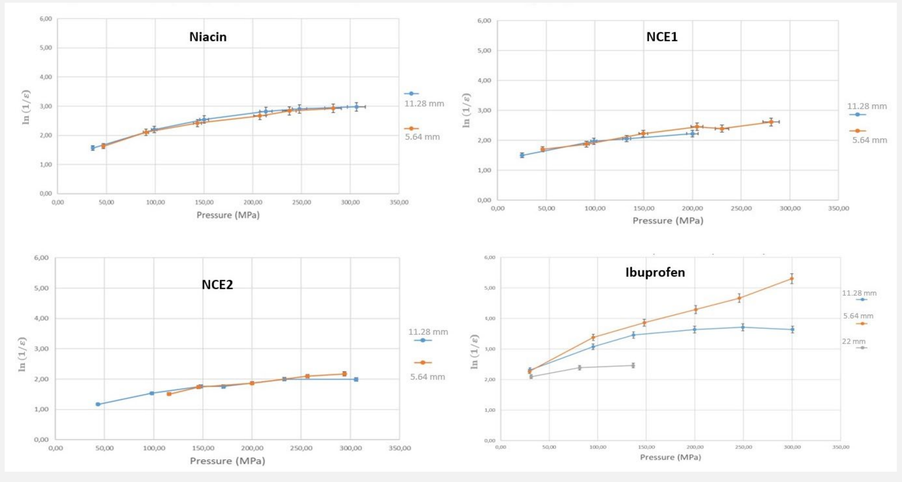
According with the characterization data presented in Table 2, the four active ingredients selected for this study have quite different particle size distribution: NCE1 is the coarsest powder, niacin and ibuprofen are fine powder and NCE2 is micronized. Surface area seems to have no direct correlation with the measured size distributions, only niacin has a value significantly bigger than ibuprofen, NCE1 and NCE2. On the other hand, ibuprofen shows true density value significantly smaller than those of the other three actives.

The correlation coefficients (R2, Table 2) of the compressibility regressions range from 0.922 to 0.979 indicating reliability of the Heckel linear fitting and of the derived Py value for all the compaction tests conducted.
Interestingly for the purpose of this work, the Heckel plots (Figure 1) and Py values (Table 2) obtained with tooling of different diameters were equivalent for three out of four tested active ingredients.

Active ingredient	True density (g/cm³)	d10 (µm)	d50 (µm)	d90 (µm)	SPAN	Surface area (m²/g)	Tooling diameter (mm)	Heckel P_y value (MPa)	Linearity pressure range (MPa)	Heckel linear fitting (R^2)
Niacin	1.4664 ± 0.0011	5.12 ± 0.14	20.24 ± 0.33	69.93 ± 1.01	3.2	0.533 ±0.0037	5.64	169	90.6-237.6	0.960
							11.28	161	36.0-213.5	0.951
NCE1	1.366 ± 0.0002	8.00 ± 1.05	103.77 ± 5.44	291.98 ± 11	2.75	0.206 ±0.0443	5.64	254	46.2-280.8	0.959
							11.28	244	25.1-200.0	0.929
NCE2	1.5159 ± 0.0019	1.39 ± 0.01	4.66 ± 0.03	13.46 ± 0.11	2.59	2.46 ±0.0644	5.64	280	115.7-293.9	0.969
							11.28	237	43.2-232.9	0.955
Ibuprofen	1.1144 ± 0.0006	12.17 ± 0.23	36.27 ± 0.42	81.50 ± 1.67	1.9	0.23 ±0.0077	5.64	95	29.7-299.6	0.979
							11.28	126	30.2-199.5	0.922
							22.00	171	31.4 and 81.3*	1.000*

Tab.2 - Results of characterization tests and Heckel analysis conducted on the four investigated active ingredients.

Figure 1 - Heckel profiles of the four tested active ingredients obtained with tooling of different diameters.



Indeed, only ibuprofen Heckel profiles result dependent on the tooling type, with Py value increasing with the increase of tooling diameter (behavior confirmed using also 22 mm tooling).
Although the available data does not allow robust explanation of the ibuprofen behavior, it could be reasonably assumed that this active ingredient has a compression behavior significantly different than that of niacin, NCE1 and NCE2. Its Py value obtained with 5.64 mm and 11.28 mm tooling is at least 40 MPa smaller than that of other actives, indicating a more plastic behavior than other actives.
This will be further investigated in future works.

CONCLUSIONS

Determination of compressibility profile seems in most cases not dependent from diameter of the tooling used to compact the powder under evaluation; but attention must be paid to materials deviating from this behavior.

Work will be conducted in future to understand if active ingredients deviating from tooling size independence could be identified according with their physical-chemical and solid-state properties.

REFERENCES

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