QbD in paediatric formulations.

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INTRODUCTION

Obtaining formulations for paediatric diseases is one of the major challenges to face in the coming years. EMA, in the Guideline on pharmaceutical development of medicines for paediatric use [(1)] said in the General considerations: *Any medicine should be designed to meet patient needs and to consistently deliver the intended product performance. A systematic approach to the pharmaceutical development in accordance with ICH Q8 could be followed in order to meet these objectives. When applied, the quality target product profile (QTPP) should be established taking into consideration the specific needs of the paediatric population. Based on the QTPP the critical product quality attributes (CQAs) should then be identified as well as the formulation and process parameters that may affect them. This approach will help defining the pharmaceutical design of the paediatric medicinal products.*

One of the indicated administration routes for paediatric patients is the oral [(1)], proposing the orodispersible tablets as an appropriate formulation. There are different technologies for their production, however, direct compression has the most relevant economic interest among drug manufacturers. The correct choice of excipients and their CMA (Critical Material Attribute), according to their function in the formula, is one of the aspects to consider as part of the product drug CQA.

Considering the methodology SeDeM[(2)], it is proposed as CMA the compressibility and flowability indexes calculated for the major excipient chosen during the development to improve the index of compressibility of the API. These CMA designated could be considered as specification to control the variability in the excipient during routinary production due to its importance in the uniformity dosage in paediatric products.

As an example of the proposed methodology, an excipient processed to be used in direct compression, Excipress GR150® (Lactose monohydrate), has been analyzed.

EXCIPIENT CHARACTERIZATION USING THE SeDeM METHOD

The SeDeM method is based on the experimental study and quantitative determination of the characterization parameters of powdered substances that provide the necessary information about substance's appropriateness for obtaining tablets by direct-compression technology. The considered parameters are as follows:

- Bulk density (Da)
- Tapped density (Dc)
- Inter-particle porosity (Ie)
- Carr index (IC)
- Cohesion index (Icd)
- Hausner ratio (IH)
- Angle of repose (α)
- Flowability (t")
- Loss on drying (%HR)
- Hygroscopicity (%H)
- Particle size (%Pf)
- Homogeneity index (IH)

Definition of characterization parameters

Whenever possible, the methods indicated in pharmacopoeias were applied. If not available, a system based on the usual practice in galenic research was proposed, adapted specifically for the SeDeM Diagram.

- Bulk density (Da): In accordance with the method described in Section 2.9.15 of Eur. Ph.
- Tapped density (Dc): According to the method described in Section 2.9.15 of Eur. Ph.
- Inter-particle porosity (Ie): Ie = Dc –Da / DcxDa
- Carr index (IC%): This is calculated from Da and Dc as: IC=(Dc _ Da / Dc)x100
- Cohesion index (Icd): The cohesion index is determined by directly compressing the product under study. Determine the hardness (N) of the tablets obtained. Calculate the mean hardness obtained.
- Hausner ratio (IH): This is calculated from Da and Dc as: IH= Dc / Da
- Angle of repose: This is the angle of the cone formed when the product is passed through a funnel with the following dimensions: funnel height 9.5 cm, upper diameter of spout 7.2 cm, internal diameter at the bottom, narrow end of spout 1.8 cm. Calculate the angle tangent value (a) of the cone by using the following equation: $Tg(\alpha) = h / r$.
- Flowability (t"): In accordance with the method described in Section 2.9.16-2 of Eur. Ph.

• Loss on drying (%HR): This is determined by the losson-drying test carried out in accordance with General method 2.2.32 in Eur. Ph.
• Hygroscopicity (%H): Determination of the sample weight increase after being kept in a humidifier at ambient relative humidity of 76% (±2%) and a temperature of 22 _C ±2 _C for 24 h.
• Percentage of particles measuring <50µ (%Pf): particle size is determined by means of the sieve test in accordance with the General method 2.9.12 of Eur. Ph.
• Homogeneity index (IΘ): In accordance with the general method described in General method 2.9.12 of Eur. Ph.
The next step is to convert the numeric limits for each SeDeM parameter to radius values r. At the end, Mean Incidence values and Good Compressibility Index will be considered as a CMA[(2)].

EXCIPRESS GR150® characterization

Using SeDeM method, **EXCIPRESS GR150®** (Lactose monohydrate) was characterized, obtaining the following results, in three different batches:

	1(*)	2(*)	3(*)	Mean
Da	6,36	6,42	6,00	6,26
Dc	7,67	7,52	7,14	7,44
Ie	2,24	1,90	2,22	2,12
IC	3,42	2,93	3,19	3,18
Icd	9,10	10,00	10,00	9,70
IH	8,97	9,15	9,05	9,06
(α)	4,96	5,09	5,14	5,06
t"	9,00	9,00	9,00	9,00
%HR	9,30	8,88	9,46	9,21
%H	10,00	10,00	9,98	9,99
%Pf	7,19	7,19	7,39	7,26
IΘ	3,65	2,85	4,30	3,60

(*)1: Batch P1068GX1, 2: Batch P1062GX1, 3: Batch P1038GX.

Table 1. SeDeM experimental radius values results for EXCIPRESS GR150®

	1(*)	2(*)	3(*)	Mean
Dimension	7,02	6,97	6,57	6,85
Compressi-bility	4,92	4,94	5,14	5,00
Flowability	7,64	7,74	7,73	7,70
Lubricity/ Stability	9,55	9,44	9,72	9,57
Lubricity/ Dosage	5,42	5,02	5,85	5,43

(*)1: Batch P1068GX1, 2: Batch P1062GX1, 3: Batch P1038GX.

Table 2. SeDeM Mean Incidence values for EXCIPRESS GR150®

	1(*)	2(*)	3(*)	Mean
IGC	6,49	6,42	6,57	6,49

(*)1: Batch P1068GX1, 2: Batch P1062GX1, 3: Batch P1038GX.

Table 3. SeDeM Good Compressibility Index for EXCIPRESS GR150®

and SeDeM diagrams were obtained as follow:

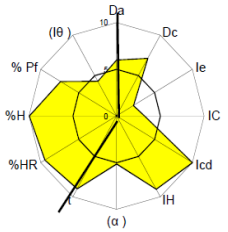

Figure 1. SeDeM diagram for EXCIPRESS GR150® Batch P1038GX.

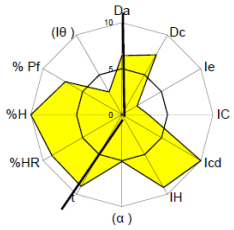

Figure 2. SeDeM diagram for EXCIPRESS GR150® Batch P1062GX1

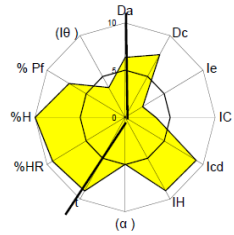

Figure 3. SeDeM diagram for EXCIPRESS GR150® Batch P1068GX1

The diagram shows good properties of compressibility and powder flow for EXCIPRESS GR150® that can help to active ingredients or formulas with problems in these aspects.

CONCLUSIONS

1.- Considering twelve galenic parameters, the SeDeM method allows the excipients characterization and defines its strong points to consider during the product formula design, specially on compressibility and flowability index.
2.- Compressibility and Flowability index should by characterizated as CMA (Critical Material Attribute) during I+D process in paediatric formulations using SeDeM method, to control orodispersible tablets uniformity of dosage during the manufacturing process.
3.- In order to keep under control the uniformity of dosage during the manufacturing process of the formula, the excipient routinary results for compressibility index and flowability index should be near to the experimental values observed. The deviation will be specified considering the excipient variability observed during the experimental tests.
4.- To EXCIPRESS GR150® for Compressibility index a value of 5.0 (-5%) and a value of 7.7 (-5%) for Flowability index were proposed as CMA.

REFERENCES

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2. 2. Suñé-Negre JM, Roig M, Fuster R, Hernandez C, Ruhi R, Garcia-Montoya E, et al. New classification of directly compressible (DC) excipients in function of the SeDeM Diagram Expert System. Int J Pharm. 2014;470(1–2):15–27.