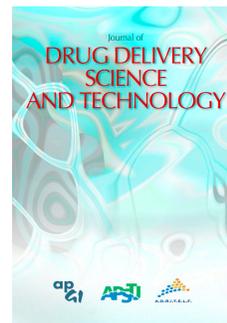


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Newly designed punch for scored tablets: evaluation by an expert system based on Quality by Design

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ABSTRACT

Scored tablets enable modulation of the drug dose and intake by elderly, pediatric and dysphagic patients. However, they are known to involve difficulties in splitting, problems of mass uniformity of portions and loss of mass on breaking. A new punch designed for manufacturing of convex-faced cylindrical easy-breakable tablets (EBTs) was proposed. The upper punch exhibited a pronounced cross ridge and two curvatures, the peripheral one having lower radius, to allow a section of small area to be split and better exploitation of the applied force. Punches of 8 mm in diameter were used for manufacturing of orally disintegrating tablets (ODTs), and four of the most common co-processed ODT excipients were employed to explore the versatility of the investigated punch. For this purpose, an expert system was constructed based on 10 selected critical quality attributes, namely bulk density, compressibility index and cohesion index of the powder formulations as well as mass uniformity, crushing strength, friability, breakability index, disintegration time, wetting time and percentage water uptake of the tablets. Experimental data relevant to these parameters were normalized to radius values in a 0-10 range, 5 being the minimum acceptable. By connecting such normalized values, radar diagrams were drawn. The relevant area and shape along with the calculated indices of overall quality pointed out suitability and robust performance of the EBT punch used for ODT manufacturing.

Keywords: Tablet Punch, Scored Tablets, Easy Breakable Tablets, Orally Disintegrating Tablets, Co-processed Excipients, Expert System, Quality by Design

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INTRODUCTION

Scored tablets could offer major advantages, such as primarily easier administration to the elderly, children or patients who have difficulty in swallowing, dose flexibility for personalized drug strength and consequently possible reduction of healthcare costs [1–5].

There are different modes of splitting tableted dosage forms, mainly by using a tablet splitter or by manually breaking units with one or more indentation lines into two, three or four portions. Frequently, when incisions are not present, scissors or knives are also used.

The most important quality attributes for scored tablets are easiness of subdivision along the score lines, mass uniformity of the obtained portions and limited loss of mass following splitting.

Uneven breaking of tablets may result in fluctuations in the administered dose, and this may be clinically important with serious repercussions especially in the case of drugs having a narrow therapeutic range.

High percentages of patients perceiving scored tablets as having critical splitting behavior were reported in the literature, with related non-compliance issues [4–6]. The negative evaluation on breakability of scored tablets was a generally encountered problem, many tableted drug products exhibiting dysfunctional score lines. In particular, difficulties in splitting, unequal breaking and excessive loss of mass after breaking were broadly observed. Characteristics of the tablets, such as size, shape, hardness and geometry of indentation lines, were all shown to have an important impact on how easy and properly a tablet could be broken.

Therefore, a need for improvement of the functioning of score lines was generally highlighted. In this context, the possibility of having punches with a geometry suitable for the production of scored tablets easily and precisely splittable would prove highly useful.

Based on these premises, the aim of the current study was to propose the use of a new punch designed for manufacturing of convex-faced cylindrical easy-breakable tablets (EBTs) and evaluate its performance.

The new punch was available in 8, 12 or 16 mm diameter, with either single or double orthogonal score lines, the smallest diameter being reported to be the minimum still allowing for manageability of breakable tableted units [5–7]. Among these configurations, the 8 mm punch with cross lines, *i.e.* provided with the indentation having higher complexity, was employed in that it was expected to increase the technical difficulties to be faced within the investigation representing the worst possible case.

Orally disintegrating tablets (ODTs) were used as a model dosage form for the study conduct. Indeed, they are known to pose special challenges due to the need for balancing mechanical properties with a suitable extent of porosity. This is required to enable fast disintegration in the mouth cavity and could be obtained by application of only relatively low compression forces.

In order to more broadly test the potential of the novel punch, *placebo* ODTs were prepared from a number of purposely marketed co-processed excipients chosen out of the most commonly employed ones. The use of different powder formulations would have allowed to investigate whether the peculiar geometry and size of the punch combined with the physico-technological and specific properties of the selected excipients could result in manufacturing of compressed tablets endowed with overall satisfactory quality profile. The processed powders and the obtained tablets were subjected to physico-technological characterization, including evaluation of bulk density, flowability, cohesion on the one hand, and hardness, friability, mass uniformity, disintegration, wettability and water uptake on the other.

Due to the large number of the variables involved and their possible mutual interactions, an experimental approach relying on a previously-described expert system was applied [8]. The expert system was constructed taking account of the overall properties of the powder mixtures based on each of the excipients in use and the mechanical as well as disintegration characteristics of the resulting tablets.

MATERIALS AND METHODS

Materials

Prosolv ODT G₂ was gifted by JRS Pharma (Rettenmaier Italia, Castenedolo, IT), Ludiflash by BASF (BASF Italia, Cesano Maderno, IT), Galeniq 721 by Beneo-Palatinit (Giusto Faravelli, Milano, IT), Pharmaburst 500 by SPI Pharma (Wilmington, DE, USA). Magnesium stearate was supplied by ACEF (Fiorenzuola D'Arda, IT).

Methods

Characterization of powders

Prosolv ODT G₂, Ludiflash, Galeniq 721 and Pharmaburst 500 were preliminarily evaluated for particle size distribution by sieve analysis (45, 63, 90, 125, 180, 250, 355, 500 μm; Octagon 200, Endecotts, UK sieve shaker, 5 min, amplitude 4, about 100 g sample).

Scanning Electron Microscope (SEM) photomicrographs of powder samples of ODT excipients were acquired after gold-sputtering using a plasma evaporator under vacuum, at an accelerated voltage of 5 kV at 2000x magnification (Gemini SEM 500, Carl Zeiss, CH).

Each ODT excipient was mixed with magnesium stearate before tableting, and the relevant mixtures were evaluated for bulk density (Db) in a 250 mL glass cylinder (about 100 g sample) and compressibility index (Com) (STAV 2003, Jel, Ludwigshafen, DE).

Manufacturing and characterization of tablets

Powder blends composed of ODT excipient (98.50%, w:w) and magnesium stearate (1.50%, w:w) were obtained by Turbula mixer (Willy A. Bachofen, Muttensz, CH; 5 min, 200 rpm).

200 mg of each powder mixture was tableted by a rotary instrumented tablet press (AM8S, Officine Meccaniche Ronchi, Cinisello Balsamo, IT) equipped with the punch under investigation for easy breakable tablet production (EBT punch, B&D Italia, Carate Brianza, IT, Ø 8 mm). The equipment was set so as to obtain tablets having crushing strength included in a 35-70 N range, compression force (Fa) ranging from 6 to 10 kN and maximum height of the units from 3.92 to 4.20 mm. Crushing tests were conducted in two different ways in order to measure diametral crushing strength (Fcd) and axial crushing strength (Fca) (n=10). For Fcd measurement, a single tablet was placed horizontally between the jaws with the non-indented face laid on the stainless steel surface of the crushing tester (TBH-28, Erweka, Langen, DE) and one score line oriented in the same direction as the force applied (Figure 1). For Fca, a single tablet was placed vertically between the jaws with the scored face toward the static jaw of the equipment [9]. From Fcd and Fca, cohesion index (Coh) and breakability index (Bre) were calculated as shown in eq. 1 and 2, respectively [10,11].

$$\text{Coh} = \text{Fcd} / \text{Fa} \cdot 10^5 \quad \text{eq. (1)}$$

$$\text{Bre} = \text{Fca} / \text{Fa} \cdot 10^5 \quad \text{eq. (2)}$$

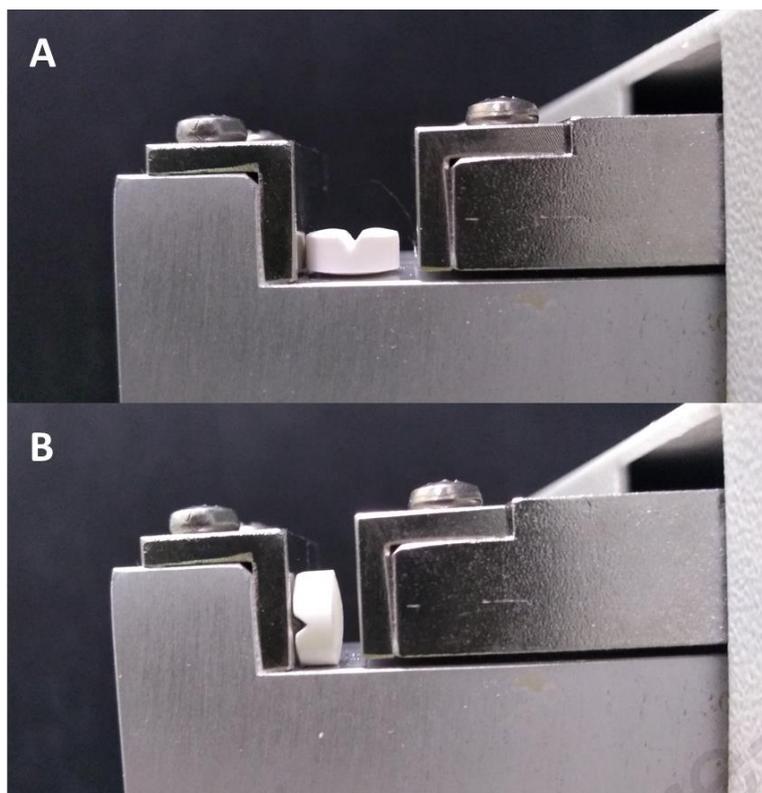


Figure 1: tablet positioning between the jaws of the crushing tester (TBH-28, Erweka, Langen, DE) for measurement of diametral crushing strength (F_{cd}) (A) and axial crushing strength (F_{ca}) (B)

The tablets were evaluated for uniformity of mass (UMT), friability (Fri) (friabilometer TA3, Erweka, Langen, DE) and disintegration time (DT) (disintegration apparatus DT3, Sotax, Aesch, CH) according to the European Pharmacopoeia. Wetting time (WT) was assessed by visual detection as the time needed to reach and dissolve approximately 2 mg of methylene blue added to the upper surface of a tablet placed on a wet paper tissue in a Petri dish (11 cm diameter, 15 g water, $n=3$) [12–14]. Percentage water uptake (PWU) was calculated as the percentage weight gain of a tablet placed on a wet paper tissue in a Petri dish until complete imbibition (11 cm diameter, 25 g water, $n=3$) [12–14].

Expert system

The study was carried out by means of an expert system relying on previous reports [15–17].

Experimental data were normalized to radius values in a 0-10 range, 5 being the minimum acceptable value (MAV). Radar diagrams were drawn by connecting the calculated radius values [15]. All radii had the same origin point, *i.e.* 0 in the normalized 0-10 scale, and were separated by a $360^\circ/n$ angle, where n is the number of parameters involved. In case all radius values were equal to

10, the radar diagram would take on a regular polygon shape, inscribed in a circumference of radius 10.

After experimental data relevant to the selected parameters had been collected, connection of calculated radius values led to drawing in a radar chart of polygons with shape and area describing the overall quality of the formulations.

As further indices of quality, Parameter Index (PI) and Quality Profile Index (QPI) were calculated by combining the normalized values of parameters [15].

Parameter Index (PI) is the ratio between the number of parameters having values \geq MAV (nP_a) and total number of parameters considered in the study (nP_t), as described by the following equation:

$$PI = nP_a / nP_t \quad \text{eq. (3)}$$

$PI \geq 0.5$ indicated acceptability.

Quality Profile Index (QPI) is the average radius value (r) multiplied by the reliability factor (f), *i.e.* the ratio between the area of the regular decagon inscribed in the circumference and the area of the circumference itself. f increases as the number of parameters increases, and so does the reliability of the method. $QPI \geq 5$ indicated acceptability [18].

RESULTS AND DISCUSSION

Novel punch design

Punches and dies are key elements of the tableting process. As they are responsible for the size and shape of the tablets, they need to be designed and produced with high precision and accuracy [19,20]. The new type of punch was devised in order to obtain scored tablets with improved performance in terms of easiness of breakup, uniformity of portion mass and low loss of mass following splitting.

A special geometry of the upper punch was indeed conceived, encompassing a pronounced cross ridge and double curvature (Figure 2). This would involve a particular pattern of compaction force transmission, possibly leading to tablet domains of different density [5].



Figure 2. Upper EBT punch (right) with relevant lower punch (left) and die (B&D Italia, Carate Brianza, IT; \varnothing 8 mm).

The layout of the resulting EBT is shown in Figure 3. The scored tablet face was endowed with two curvatures of different radius and especially deep cross lines. The more pronounced curvature, *i.e.* that having lower radius, was externally positioned. The particular indentation was aimed to give a section of smaller area to be fractured, which was expectedly associated with reduced mechanical resistance to splitting. In addition, the complex curvature pattern of the scored tablet face was such as to increase the distance between the two opposite points of application of effort. This resulted in longer lever arms enabling more efficient exploitation of the force applied.

The lower punch exhibited a traditional geometry with a single curvature radius and no indentations.

Overall, the innovative design of the dosage form would allow the tablet to be split when laid on a solid plane surface through application of a reduced extent of force with a fingertip. This would not only reflect in more convenient splitting, but also could limit the problems related to mass reproducibility of the resulting portions, due to sharper and less stressful breakup of the tablet.

Punches with complex shape and thin ridges can withstand relative low compression forces. In particular, according to the manufacturer's specifications, the 8 mm EBT punches would allow for use of compression forces up to 15.6 kN. However, given the limited hardness properties that are pursued with ODTs, such a force threshold would represent a minor limitation in this case. On the other hand, due to the geometry of the ridged face, sticking of the powder formulation to the upper punch could be anticipated [21,22].

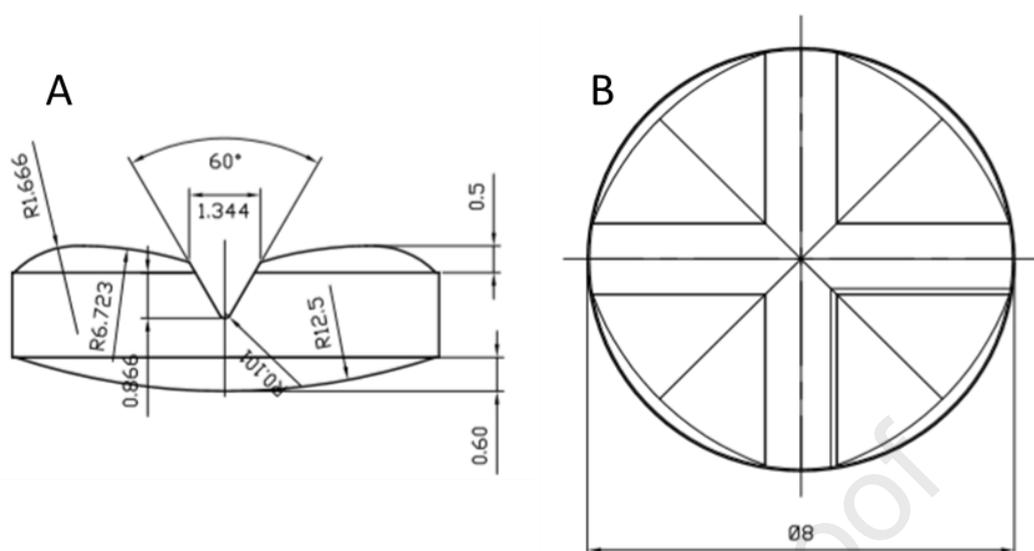


Figure 3. Schematic representation of a scored tablet fabricated using the 8 mm EBT punch. Side (A) and top (B) views (dimensions are expressed in mm).

Powder formulations

Different commercially available co-processed ODT excipients, *i.e.*, Galeniq 721, Ludiflash, Pharmaburst 500 and Prosolv ODT G₂, were selected for use as the main component of *placebo* formulations, in order to assess the new punch versatility.

In Table 1, the quali-quantitative composition and the particle size of these excipients are reported [23,24]. Ludiflash, Pharmaburst 500 and Prosolv ODT G₂ are all based on a soluble polyol, mannitol, and a superdisintegrant, crospovidone, to enable both active and passive mechanisms of tablet disintegration [25]. On the other hand, GalenIQ 721 only exploits a soluble material, isomalt, to make disintegration occur. SEM photomicrographs of powder samples of the ODT excipients employed are shown in Figure 4. These images highlight the structure of particles and particularly agglomeration among different components. In addition to the ODT excipient, a lubricant was needed. Through preliminary experimental trials, magnesium stearate at 1.5% w:w, turned out to provide adequately lubricated powder formulations in all cases.

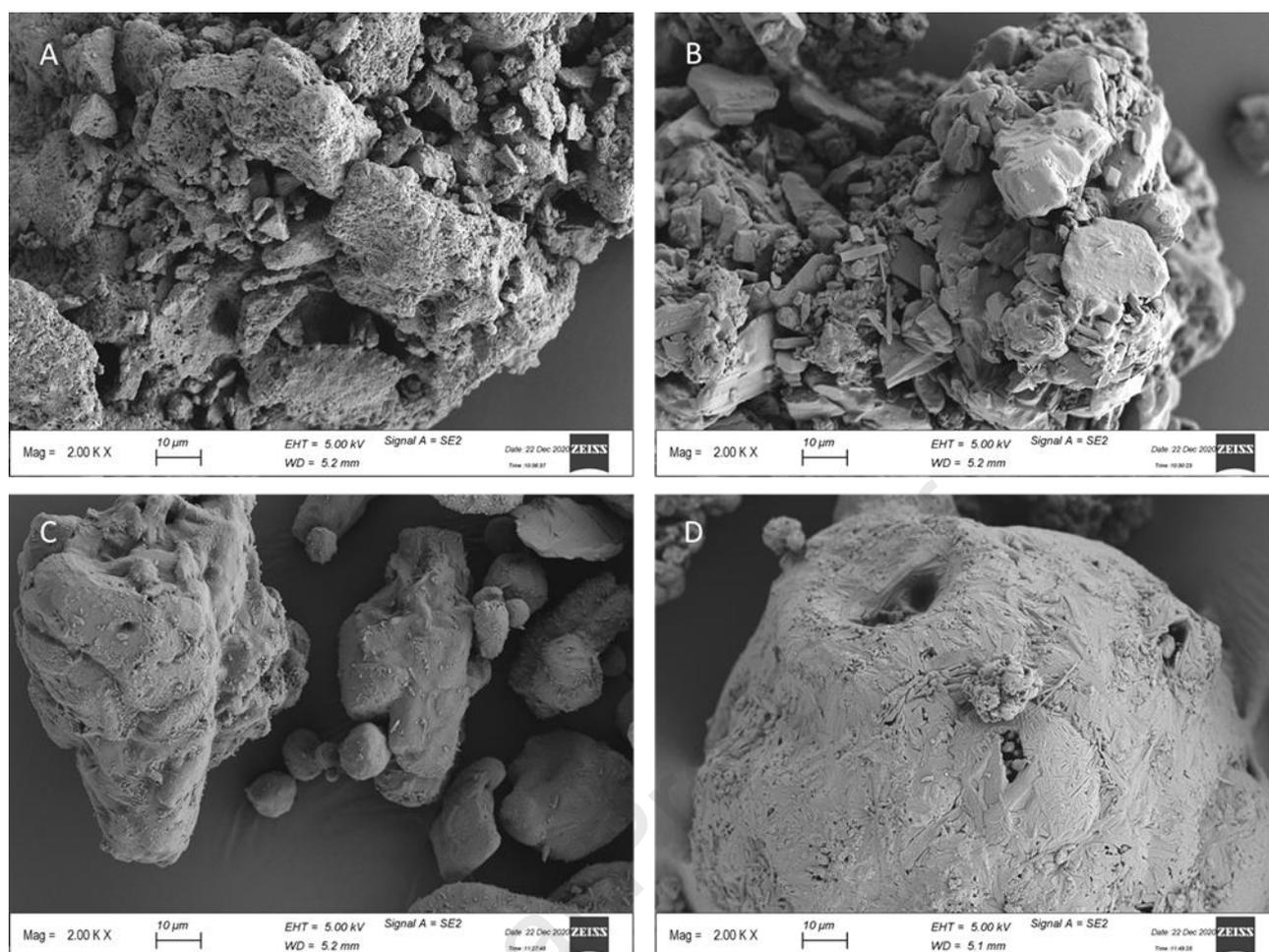


Figure 4: SEM photomicrographs of powder samples of GalenIQ 721 (A), Ludiflash (B), Pharmaburst 500 (C) and Prosolv ODT G₂ (D) (magnification 2000x).

Expert system construction

In order to evaluate the performance of the EBT punch, an expert system was applied based on criteria of Quality by Design reported in ICH-Q8, identifying the main parameters involved as Critical Quality Attributes (CQAs) [26]. In particular, to build up quality profiles of the formulations under investigation, 10 CQAs were selected, including physico-technological characteristics of the powder mixtures and mechanical as well as disintegration properties of the tablets (Table 2).

Operating ranges were defined for each parameter [15]. Such ranges were constructed around the relevant minimum acceptable value (MAV), as inferred from own experience, literature and/or compendial sources. The values lying in the defined ranges were normalized to a 0-10 scale using purposely built mathematical functions transforming them into the so-called radius values (r) (Table

2). MAV was always set at 5 in this scale. Thus, radii equal to or higher than 5 indicated suitability of the considered parameter. Experimental data lying outside the radius interval once normalized would be set equal to 0 or to 10 when negative or higher than 10, respectively.

Bulk density is an important parameter in the tableting process; the higher its value, the easier will be to fill the selected die with the established mass of powder. Values ≥ 0.5 g/mL generally turn out suitable for tableting, and this threshold was therefore considered as the MAV. According to European Pharmacopoeia, powder materials having compressibility index $\leq 25\%$ were deemed acceptable. Based on expertise gained in ODT manufacturing and on reportedly acceptable tablet hardness values, crushing strength ≥ 35 N, and cohesion and breakability indices both ≥ 200 were regarded as appropriate [27]. Indeed, through preliminary trials, these values were found to allow sufficient mechanical characteristics to be achieved on the one hand, and enable easy manual splitting on the other. Because tablets fulfill the friability test when mass loss is $\leq 1\%$, this was set as the lower threshold value. Since the theoretical weight of the tablets under investigation was 200 mg, according to European Pharmacopoeia, no more than 2 out of 20 mass data could exceed the range of $\pm 7.5\%$ around the mean value and none could be outside $\pm 15\%$. Considering that, for an approximately normal distribution, the values within 2 standard deviations of the mean account for about 95% of the data (*i.e.*, 19 out of 20), it could be estimated that the tablet mass distribution would meet the mass uniformity pharmacopoeial requirement when relative standard deviation (RSD) $\leq 3.75\%$. Therefore, such an extent of data variability was regarded as the maximum tolerable. With respect to the behavior of the tableted formulations upon contact with aqueous fluids, disintegration time of 3 min was considered acceptable, as per compendial specifications. Finally, based on literature reports, the higher acceptable limit for wetting time was set at 30 s, and 50% was identified as the lower limit for percentage water uptake [13,14,28].

A series of programmed tests were performed for measurement of the identified CQAs, either involving the starting powder mixtures or the obtained tablets based on each ODT excipient employed (Table 3).

Tablet units having hardness values included in the desired range were obtained by applying compression forces in the 6-10 kN range, far lower than the maximum allowed according to manufacturer's specifications, which also led to loss of mass always $< 1\%$ upon friability testing. In addition, the relatively low compression forces used helped circumvent problems of sticking of the formulations to the upper punch.

As shown in Table 3, Prosolv ODT G₂ was endowed with the highest bulk density radius; this could be favorable in the matrix filling phase. All excipients exhibited fair flow properties. This was

also confirmed by relatively low data variability as observed in the mass uniformity test. The obtained values of cohesion index and breakability index were always higher than 500 and 300, respectively, thus appearing highly satisfactory. Disintegration time of the resulting tablets was generally lower than 3 min thus complying with pharmacopoeial requirements. Only in the case of ODTs based on GalenIQ 721, slightly slower disintegration was observed, which was completed within 5 min. Wetting time was also acceptable for all tablets except for those prepared from GalenIQ 721. A marked ability to absorb water, as indicated by percentage water uptake, was shown by all the formulations. GalenIQ 721-, Pharmaburst 500- and Prosolv ODT G₂-based ones were demonstrated to almost double their weight during the test.

Radius values calculated for each ODT formulation are reported in Table 4.

The overall quality profile associated with each ODT excipient could visually be represented by radar diagrams obtained by connecting radius values with each other inside radar charts (Figure 5).

The four decagons obtained were shown to cover a large area of the regular polygon inscribed in the circumference of radius 10, demonstrating the suitability of the EBT punches for manufacturing of ODTs using the different excipients. In the case of Prosolv ODT G₂ decagon, all vertices lay outside the regular polygon inscribed in the circumference of radius 5 delimiting the acceptability zone. Moreover, such a decagon turned out to be the most regular and displayed the broadest area.

Radius values obtained by processing the experimental data were combined to calculate Parameter Index (PI) and Quality Profile Index (QPI) (Table 5). For calculation of the latter, reliability factor was 0.935 on account of the 10 parameters that were selected.

Such indices always exhibited values ≥ 0.5 and ≥ 5 , respectively, confirming the good performance of the EBT punches when used for manufacturing of splittable ODTs.

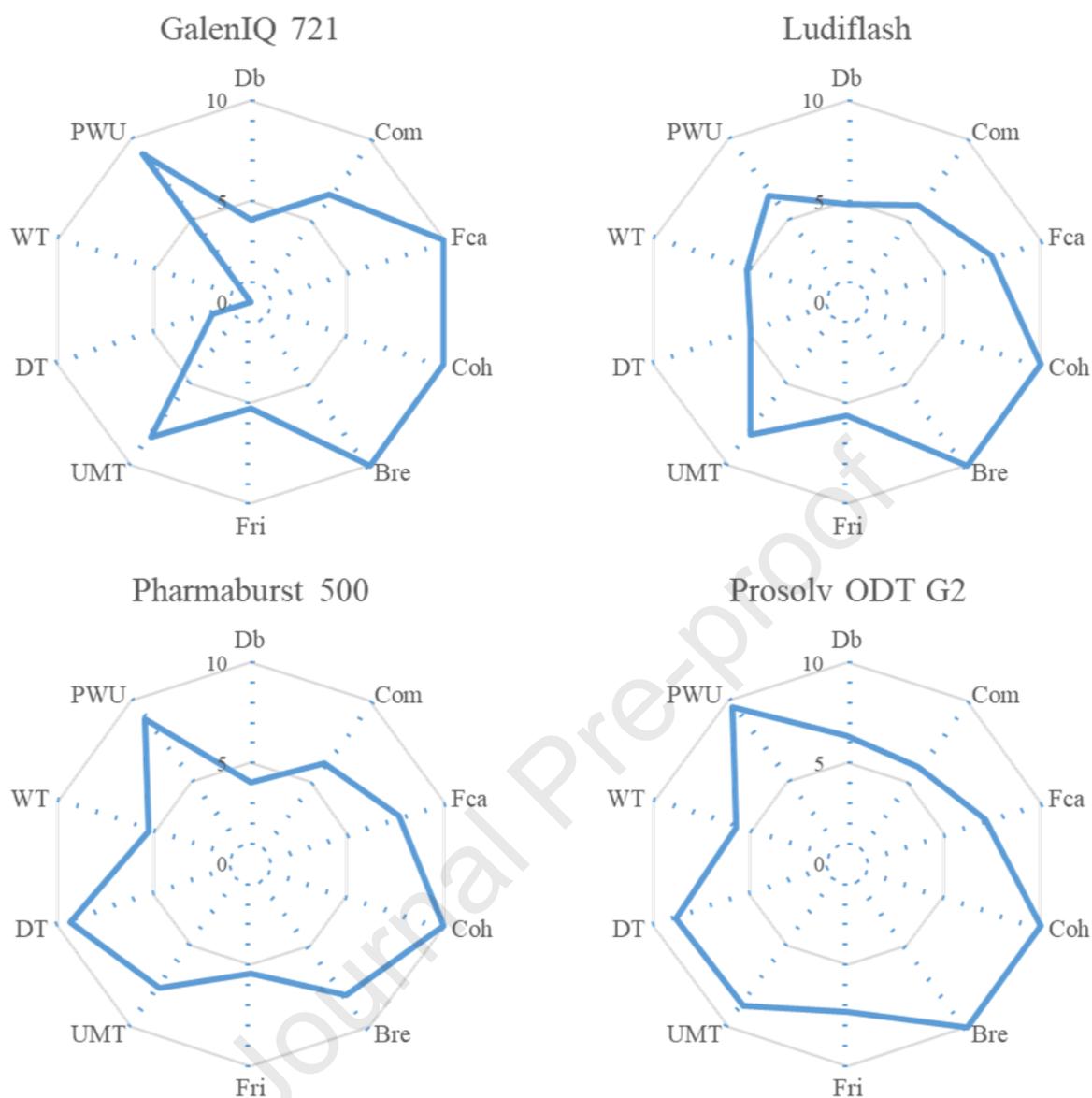


Figure 5. Radar diagrams for each ODT powder formulation drawn from calculated radius values. *Db* (Bulk density), *Com* (compressibility index), *Fca* (crushing strength), *Coh* (cohesion index), *Bre* (breakability index), *Fri* (friability), *UMT* (uniformity of mass of tablets), *DT* (disintegration time), *WT* (wetting time), *PWU* (percentage water uptake).

CONCLUSION

While scored tablets offer major advantages, such as easier swallowing and flexibility in the drug dose, their profitable use is known to be hampered by issues mainly associated with difficulties in breakup along the indentation lines, lack of mass uniformity for the obtained portions and loss of

mass following splitting, possibly bringing about fluctuations in the administered dose. Therefore, the present work was focused on the study of a new punch purposely designed for manufacturing of convex-faced cylindrical easy-breakable tablets (EBTs).

The scored tablet face was endowed with especially deep cross lines and double curvatures, enabling a section of smaller area to be fractured on the one hand, and more efficient exploitation of the applied force on the other due to increased length of lever arms.

In view of the critical need for balancing mechanical properties with a suitable extent of porosity, orally disintegrating tablets (ODTs) were used as an especially challenging model dosage form. Among co-processed ODT excipients, four of the most commonly employed ones were selected in order to explore the versatility of the investigated punch.

Because of the large number of variables involved, an expert system was constructed taking account of 10 critical quality attributes encompassing physico-technological properties of the powder mixtures and mechanical as well as disintegration characteristics of the resulting tablets.

Radar diagrams drawn for each ODT formulation and relevant indices of overall quality demonstrated suitability of the investigated EBT punch for the intended use and robust performance irrespective of the materials subjected to tableting. Although Prosolv ODT G₂ was the highest in rank, the EBT punch allowed ODTs provided with satisfactory quality profile to be manufactured by direct compression from all the excipients employed.

Based on the satisfactory results obtained in this preliminary study, the performance of the new EBT punch will undergo evaluation *versus* a traditionally designed indented punch, particularly in terms of ease and accuracy of subdivision of the resulting tablets.

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Journal Pre-proof

Newly designed punch for scored tablets: evaluation by an expert system based on Quality by Design

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Table 1: composition and particle size of the co-processed ODT excipients employed [23,24]

ODT excipient	Composition	particle size: median (IQR*)
GalenIQ 721	75% 6-O- α -D-Glucopyranosyl-D-sorbitol (1,6-GPS) and 25% 1-O- α -D-Glucopyranosyl-D-mannitol dihydrate (1,1-GPM)	143 (102) μ m
Ludiflash	90% D-mannitol, 5% Kollidon CL-SF (crospovidone), 5% Kollicoat SR 30D (polyvinyl acetate dispersion)	134 (75) μ m
Pharmaburst 500	85% mannitol, <10% silicon dioxide, <10% sorbitol, 5% crospovidone	107 (43) μ m
Prosolv ODT G ₂	60-70% mannitol, 15-20% microcrystalline cellulose, <10% fructose and silicon dioxide, 5% crospovidone	70 (64) μ m

* IQR, interquartile range.

Table 2. Operating ranges and normalized radius intervals for the selected Critical Quality Attributes (CQAs) along with functions used to transform experimental values (v) into normalized radius values (r).

CQAs		Operating range	Radius interval*	Normalization function
Bulk density	Db	0-1 g/mL	0-10	$10v$
Compressibility index	Com	0-50%	10-0	$(50-v)/5$
Crushing strength	Fca	0-70 N	0-10	$v/7$
Cohesion index	Coh	0-400	0-10	$v/40$
Breakability index	Bre	0-400	0-10	$v/40$
Friability	Fri	0-2%	10-0	$(2-v)/2 \cdot 10$
Uniformity of mass of tablets	UMT	0-7.5%	10-0	$(7.5-v) \cdot (10/7.5)$
Disintegration without disk	Dis	0-6 min	10-0	$(1-v/360) \cdot 10$
Wetting time	WT	0-60 s	10-0	$(1-v/60) \cdot 10$
Percentage water uptake	PWU	0-100%	0-10	$v/10$

* better experimental results correspond to high values within 0-10 intervals and to low values within 10-0 ones, respectively

Table 3. Experimental values of the investigated Critical Quality Attributes (CQAs) for each ODT powder formulation.

	GalenIQ 721	Ludiflash	Pharmaburst 500	Prosolv ODT G₂
Bulk density (g/mL)	0.409	0.485	0.406	0.633
Compressibility index	17.0	20.4	19.2	20.2
Crushing strength (N)	71	52	54	50
Cohesion index	906	683	551	888
Breakability index	1227	1058	320	1122
Friability (%)	0.95	0.87	0.91	0.54
Uniformity of mass of tablets (%)	1.29	1.42	1.79	0.96
Disintegration time (sec)	288	180	24	42
Wetting time (sec)	> 60	28.7	28.3	25.7
Percentage water uptake (%)	90.6	65.4	88.5	96.4

Table 4. Radius values of the investigated Critical Quality Attributes (CQAs) calculated for each ODT powder formulation.

	GalenIQ 721	Ludiflash	Pharmaburst 500	Prosolv ODT G₂
Bulk density (Db)	4.09	4.85	4.06	6.33
Compressibility index (Com)	6.60	5.92	6.16	5.96
Crushing strength (Fca)	10	7.43	7.71	7.14
Cohesion index (Coh)	10	10	10	10
Breakability index (Bre)	10	10	8.00	10
Friability (Fri)	5.25	5.65	5.45	7.30
Uniformity of mass of tablets (UMT)	8.28	8.11	7.61	8.72
Disintegration time (Dis)	2.00	5.00	9.33	8.83
Wetting time (WT)	0.00	5.22	5.28	5.72
Percentage water uptake (PWU)	9.06	6.54	8.85	9.64

Table 5. Indices of overall quality calculated for each ODT powder formulation.

	GalenIQ 721	Ludiflash	Pharmaburst 500	Prosolv ODT G ₂
Profile Index (PI)	0.60	0.90	0.90	1.00
Quality Profile Index (QPI)	6.10	6.42	6.78	7.45

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.