European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 638–648

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Predicting orally disintegrating tablets formulations of ibuprophen tablets: An application of the new SeDeM-ODT expert system

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ARTICLE INFO

Article history:
Received 4 November 2011
Accepted in revised form 21 December 2011
Available online 5 January 2012

Keywords:
IGCB
Disintegrant
SeDeM-ODT
Preformulation
Bucodispersible tablets
Direct compression (DC)

ABSTRACT

This article provides a new innovative tool for pharmaceutical preformulation to predict whether a disintegrant excipient or mixture of powder containing API + excipients is suitable to obtain a bucodispersible tablet by direct compression or not.

This innovative tool is the new model SeDeM-ODT that provides the Index of Good Compressibility and Bucodispersibility (IGCB index), which is based on the previous SeDeM expert system that indicates the aptitude of a powder to be compressed. The IGCB index is composed of six main factors (from 15 pharmaceutical raw parameters), which indicate whether a mixture of powder has the aptitude to be compressed by direct compression and at the same time indicates whether these tablets are suitable to be used as a bucodispersible tablet (disintegration time lower than 3 min).

1. Introduction

Orally disintegrating tablets are dosage forms formulated to improve a pharmaceutical product respect to his disintegrating and dissolution rates. In order to achieve rapid disintegration rate, the tablet formula must provide a high porosity, low density and a low hardness [1]. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased, as it has significant impact on the patient compliance [2]. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that dysphagia (difficulty in swallowing) [3] is common among all age groups of people, but it is more specific in pediatric and geriatric population [4]. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Orally disintegrating tablets are also called orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts [5,6]. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as orally disintegrating tablets or ODTs [7]. Recently, European Pharmacopoeia has used the term "Orodispersible tablet" for tablets that disperses readily and within 3 min in mouth before swallowing [8]. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue" [7].

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include [9–12], as ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients [9–12]; no risk of obstruction of gastrointestinal tract by the dosage form, which is beneficial for traveling patients who do not have access to water, easy administration for pediatric, geriatric, and inpatients (specially for mentally retarded and psychiatric patients); the rapid disintegration of the tablet results a quick dissolution of the drug and fast absorption that provide rapid onset of action [13]; bioavailability of drugs that are absorbed in the mouth, pharynx, and esophagus is increased [14–16]; and pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increases the bioavailability of the drug [17].

Various processes are employed to obtain ODT tablets, such as lyophilization, molding, cotton candy process, spray drying, mass extrusion, compaction, and other patented technologies [2]. However, the most interesting way for the pharmaceutical industry is obtaining bucodispersible tablets by direct compression because it is a cheaper and shorter process, since no high technologies machines are required.

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doi:10.1016/j.ejpb.2011.12.012

This article proposes a new innovative expert system called "SeDeM-ODT," which helps to determine the property of excipients to be used to obtain orally dispersible tablet (ODT) by direct compression technology. This expert system is based on the previous SeDeM expert system, which predicts the aptitude of a mixture of powder to produce conventional tablets by direct compression [18–23]. This expert system is unique, since it provides an ODT formulation taking into account the type of components and also a recommendation based on the intrinsical properties of them that derive from the characteristics and morphology of the particles so that they provide accurate information. Therefore, the proposed formulation will have a high probability to be successfully compressed and to have a fast disintegration. The formulation provided undergoes direct compression, which has many advantages under a productive point of view, while reducing the number of steps during the development process (avoiding granulation). The objective of this study is to demonstrate the validity of the new tool for developing ODT tablets, which would meet the specifications for ODT tablets.

In addition, the expert system has the advantage to provide formulations with the lowest quantity of excipients, with only 1 excipient combined with the API and the formula standard of lubricants, avoiding other unnecessary excipients as for example diluents.

The provided information about the formulation can be used in the final analysis for a better process understanding when a Quality by Design development is being carried out. Therefore, this innovative tool is aligned with the actual requirement of the regulatory health authorities such as FDA and ICH.

2. Characterization of powders using the SeDeM-ODT method

The rational to develop the ODT formulation will be to characterize the candidate excipients with the new tool (as we have made the previous characterization with the previous tool SeDeM, we know the IGC index (index of good compressibility)) for 42 excipients and active ingredients, so from the 42 excipients [21] we have chosen only the 8 disintegrants with the best characteristics for compression, which means they have an index of good compressibility (IGC) near to 5 or higher. The idea is to know whether the application of the modified tool to these excipients can bring a good prediction about compressibility and bucodispersability of the tablets to be developed. In order to validate the system SeDeM-ODT, all the formulas were produced and tested in the laboratory.

The new expert system SeDeM-ODT establishes how to calculate the Index of Good Compressibility and Bucodispersibility (IGCB) for these candidates, and if it is $\geqslant 5$, it indicates that the powder could be compressed by direct compression and the tablet has good bucodispersible properties.

The SeDeM-ODT methodology is composed of six factors derived from 15 main parameters. Five of them are identical than those in the SeDeM expert system proposed by Suñe et al. previously [18–23] It has been added a new parameter called disgregability factor [see Tables 1–3].

The calculation of the five factors (dimensions, compressibility, flowability/powder flow, lubricity/stability, and lubricity/dosage) of the SeDeM tool is based on the experimental study and quantitative determination of the characterization parameters of substances in powder form that provide the necessary information about the suitability of the said substances for obtaining tablets by direct compression technology. The so-called parameters are the following: Bulk Density (Da), Tapped Density (Dc), Inter-particle Porosity (Ie), Carr Index (IC), Cohesion Index (Icd), Hausner Ratio (IH), Angle of Repose (α), Powder Flow (t''), Loss on Drying (%HR), Hygroscopicity (%H), Particle Size (%Pf) and Homogeneity Index ($I\theta$). These parameters are determined by means of the SeDeM Diagram method, based on known equations duly validated by reproducible experimental tests [18–23].

The SeDeM-ODT has a new factor: disgregability. The scientific rationale for the disgregability parameter is based on these three parameters that come to give an idea of the disintegration "per se" of the excipients. Following the previous methodology, we have chosen three tests pharmacopoeia: Effervescence (disintegration for effervescent tablets), Disintegration time with disk and Disintegration time without disk.

- Effervescence Test: According to Monograph 701 *USP32–NF27* [24] and Ph Eur ⟨0478⟩ 7th ed. [8], it is placed 1 tablet on a vessel containing 200 ml of purified water at 15–25 °C, and it is observed if the tablet is dissolved or dispersed in the water so that no agglomerates of particles remain within 5 min. It is clear that this test is not specific for bucodispersible tablets, but it is a good indicator of the behavior of a tablet when it is bucodispersible, that if a tablet disgregates fewer than 5 min, so there is a high probability that it could be a bucodispersible tablet.

Table 1
Parameters and equations used to calculate the IGCB by the SeDeM-ODT.

Factor/incidence	Parameter	Symbol	Unit	Equation
Dimension	Bulk Density	Da	g/ml	$Da = P/V_a$
	Tapped Density	Dc	g/ml	$Dc = P/V_c$
Compressibility	Inter-Particle Porosity	Ie	–	$Ie = \frac{Dc-Da}{Dc \times Da}$
	Carr Index	IC	%	$IC = \frac{Dc-Da}{Dc} * 100$
	Cohesion Index[a]	Icd	N	Experimental
Flowability/powder flow	Hausner Ratio	IH	–	IH = Dc/Da
	Angle of Repose	(α)	°	tg α = h/r
	Powder Flow	t''	s	Experimental
Lubricity/stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/dosage	Particles <50	% Pf	%	Experimental
	Homogeneity Index[b]	($I\theta$)	–	[a] $I\theta = \frac{Fm + \Delta Fmn}{100}$
Disgregability	Effervescence	DE	min	Experimental[c]
	Disintegration time with disk	DCD	min	Experimental[c]
	Disintegration time without disk	DSD	min	Experimental[c]

[a] Hardness (N) of the tablets obtained with the product in question, alone or blended with lubricants if highly abrasive.
[b] Determined particle size. In accordance with the percentages of the different particle size fractions.
[c] See Tables 2 and 3.

Table 2
Conversion of limits for disgregability factor into radio values (v).

Factor	Parameter	Limit value v	Radio	Factor applied to v
Disgregability	Effervescence	0–5 (min)	10–0	See Table No. 3
	Disintegration time with disk (DCD)	0–3(min)	10–0	
	Disintegration time without disk (DSD)	0–3 (min)	10–0	

Table 3
Calculations to obtain radios value of disgregability.

Description	Effervescence	DCD	DSD
Experimental range in minutes	0–5	0–3	0–3
Range of the Radio	10–0	10–0	10–0
r = calculation to obtain radio (X = experimental value)	$(5 - X) * 2$	$(3 - X) * 3333$	$(3 - X) * 3333$

DCD: Disintegration time with disk/DSD and disintegration time without disk.

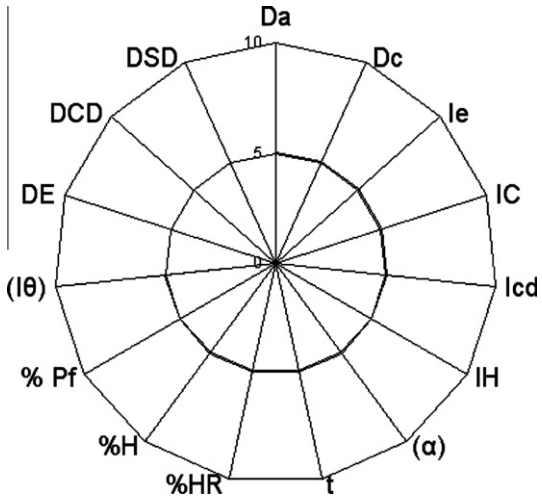

Fig. 1. Diagram SeDeM-ODT with the 15 parameters.

Additionally, this test is interesting because the media is water, which has a pH similar to saliva. According to Tables 2 and 3, the experimental values obtained will be converted into radius, with a maximum value when the disintegration is faster than 1 min, and the model will assign a value of zero when the tablet does not disintegrate in a time below or equal to 5 min.

- Disintegration Time with disk: According to Monograph 701 *USP32–NF27* [24] and Ph Eur ⟨2.9.1⟩ 7th ed [25], the specification is ⩽3 min. The specific technique is disintegration time without disk, but this test is also included, since it simulates a mechanical action inside the mouth, which will improve the disintegration of the tablets. According to Tables 2 and 3, the experimental values obtained in this test are converted into radius that follows a linear model: The higher their value is, the faster the tablets disintegrate. For those tablets that does not disintegrate in a time below or equal to 3 min, a value of 0 is assigned.

Disintegration Time without disk: According to Monograph 701 *USP32–NF27* [24] and Ph Eur ⟨2.9.1⟩ 7th ed. [25], the specification is ⩽3 min. It is a specific technique to evaluate bucodispersible tablets. According to Tables 2 and 3, the experimental values obtained in this test are converted into radiuses that follow a linear model: The higher their value is, the faster the tablets disintegrate. For those tablets that does not disintegrate in a time below or equal to 3 min, a value of 0 is assigned.

2.1. Determination of the IGCB

When all radius values are 10, the IGCB diagram has a circumscribed regular polygon shape, drawn by connecting the radius values with linear segments. The figure indicates the characteristics of the product and each parameter that determines whether or not the product is suitable to be used like bucodispersables tablets because of its good properties for compression and good disintegration characteristics. In this special case, the IGCB diagram is made up of 15 factors, which would form an irregular 15-sided polygon (Fig 1). The method also gives a numerical index to express whether the powdered substance could be used like bucodispersable tablets. In numerical form, three indexes must be calculated: the index parameter (IP) (Eq. 1), the profile index parameter (IPP) (Eq. (2)), and the Index of Good Compressibility and Bucodispersibility (IGCB) (Eq. 3)

$$\text{Index parameter(IP)IP} = \frac{N^{o}P \geq 5}{N^{o}\text{Pt}} \quad (1)$$

N° $p \geqslant 5$ = Number of parameters with a value equal or higher than 5.
N° Pt = Total number of parameters studied.

The acceptability limit would correspond to: IP ⩾ 0.5

$$\text{Index Profile Parameter(IPP)} = \text{mean r of all parameters studied} \quad (2)$$

The acceptance limit is: IPP = mean $r \geqslant 5$

Index of Good Compressibility and Bucodispersibility (IGCB) is calculated as follows:

$$\text{IGCB} = \text{IPP} \times f \quad (3)$$

where f is a reliability factor and is calculated as follows:

$$f = \text{Polygon area/Circle area}. \quad (4)$$

In this case (15 sides), f = 0971. The acceptance limit will be IGCB ⩾ 5.

Differences between IGC and IGCB will be noted when a powder has good aptitude to be compressed but bad disgregability, and in this case, the powder will have an IGC higher than 5, but when IGCB will be calculated, it will be lower than 5. On the other hand, if a powder has a good aptitude to be compressed and a good disgregability properties, the IGCB will increase respect to the IGC. Thus, the new tool (SeDeM-ODT) will select more accurately the excipients that can be used to make compressed tablets orodispersible. Besides, the new tool will select more accurately the excipients than the old SeDeM method, so that it could be used

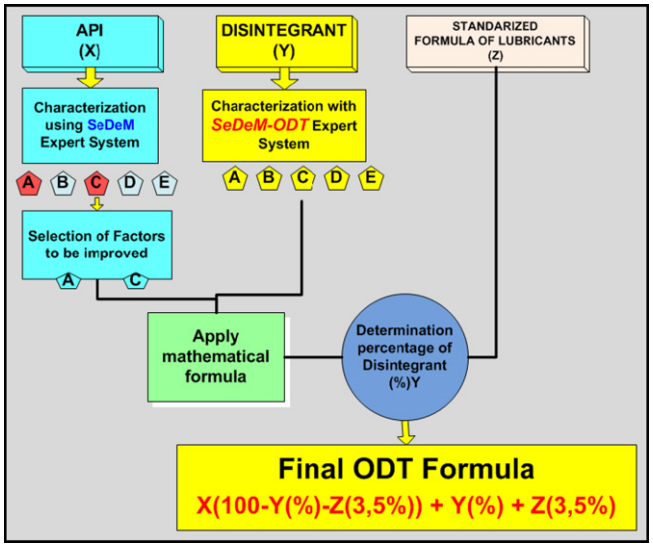

Fig. 2. Strategy proposed by SeDeM-ODT expert system to develop oral disintegrating tables (ODT). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to formulate orodispersible tablets with a single excipient that may be compressed by direct way.

2.2. Design of Idoneous ODT formulations using SeDeM-ODT expert system

As it is summarized in Fig. 2, the design of an idoneous ODT formulation must follow the next sequence:

1. Perform the characterization of the API using SeDeM expert system. The scientific rational of not using SeDeM-ODT expert system for the analysis of the API is based on the fact that it is not expected that the API has disgregability properties, although the compressibility properties must be evaluated, since bucodispersibility properties are provided by the disintegrant.
2. The disintegrants must be characterized by SeDeM-ODT expert system and choose among them those with an IGBC near or higher than 5.
3. It must be selected the worse factors obtained (all under 5), so they have to be improved by the excipient used to make the tablet. So it performed a mathematical evaluation of them according to Eq. (5), which is used for the selection of the excipient and the concentration required in order to correct the poor characteristics observed in the API. The Eq. (5) was originally designed specifically for this purpose by Suñe et al. [18–23] and is intended for use in calculating the amount of excipient required to compress the API, based on the SeDeM-ODT radius obtained for the API and the excipients.

$$CP = 100 - \left(\frac{RE - R}{RE - RP} \times 100\right) \quad (5)$$

where
CP = % of corrective excipient.
RE = mean-incidence radius value (compressibility) of the corrective excipient.
R = mean-incidence radius value to be obtained in the blend. It is recommended to have a $R = 5$ (5 is the minimum value that is regarded as necessary in order to achieve good compression).
RP = mean-incidence radius value (compressibility) of the API to be corrected.

The unknown values in Eq. (5) have been replaced with the calculated values required for each substance in order to obtain $R = 5$. Then, the CP or percentage of excipient recommended by the expert system to have de ODT tablet can be calculated.

4. The Eq. (5) will provide the percentage of excipient, which must be added to the standardized formula of lubricants proposed by Suñe et al. [18–23] composed by:

Talc	2.36%
Aerosil 200	0.14%
Magnesium stearate	1.00%

5. Finally, the remaining percentage will correspond to the API taking into account the strength required.

2.3. Materials and methods

2.3.1. Materials

Microencapsulated Ibuprophen (Model drug) (Supplier: Fagron Ibérica, Spain, Batch: 0701435, caducity date: 08/2011) is characterized by SeDeM expert system, and several disintegrants were selected (see Table 4) from a previous work [21].

2.3.2. Method

Characterization of Ibuprophen is performed using SeDeM expert system, but the characterization of eight selected disintegrants detailed in Table 4 was performed according to SeDeM-ODT expert system, in order to determine whether these excipients have orodispersible properties.

After determining the IGCB of the disintegrants, it will be evaluated those with values equal or higher than 5. SeDeM-ODT recommends those excipients which have IGCB $\geqslant 5$ to be used as unique disintegrant, which could be used alone in combination

Table 4
List of the eight selected disintegrants and API analyzed in a previous work [21].

Disintegrant	Composition	Supplier/country	Batch
AQUASORB A500®	Sodium carboxymethylcellulose	Hercules/Netherlands	51514
BRENNCEL-DIS®	Sodium Starch Glycolate	Brenntag/Spain	93090118
GLYCOLYS®	Sodium Starch Glycolate	Roquette/France	E0688
NYMCEL ZSD-16®	Sodium carboxymethylcellulose	Hercules/Netherlands	NN143051
NYMCEL ZSB-10®	Sodium carboxymethylcellulose	Hercules/Netherlands	NN1C2851
PHARMABURST C1®	Manitol + St1500 + crospovidonum + croscarmellose + SI O_2	SPI Pharma/UK	04K111
POLIPLASDONE XL®	Crospovidonum	ISP/USA	03500142748
POLIPLASDONE XL-10®	Crospovidonum	ISP/USA	03500129655
IBUPROPHEN	Ibuprophen A.S.	Fagron Ibérica, Spain	0701435

Table 5
Test results of Ibuprophen divided in five SeDeM factors.

Active product ingredient	Ibuprophen
Dimensions	3.39
Compressibility	4.46
Flowability/powder flow	1.90
Lubricity/stability	7.40
Lubricity/dosage	7.93
IGC	4.48

with the API and the standardized formula of lubricant without adding any diluents to obtain ODT tablets.

2.4. Design of the ODT formulations

After performing the characterization of the API using SeDeM expert system, it was determined that the model drug (Ibuprophen) needs to be improved on the following factors: dimensions, compressibility, flowability/powder flow (Table 5). Then, it was analyzed in detail, and it was concluded that factor flowability/powder flow did not need to be improved since it is expected to be improved with the standardized formula of lubricants [18–23].

Therefore, it was concluded that model drug needs to improve both dimensions and compressibility factors. Then, the eight disintegrants were characterized using SeDeM-ODT expert system (Table 6), and a mathematical analysis was carried out according to Eq.5 between the worst factors of the microencapsulated Ibuprophen and the same factors in each of the eight disintegrants (see Tables 7 and 8). The percentage required to obtain ODT tablets was determined with the mathematical formula.

2.5. Formulation of Ibuprophen 600mg bucodispersible tablets

To prepare bucodispersible tablets (ODTs) of Ibuprophen 600 mg with the 8 selected disintegrants, it was taken into account that the formulation to design and develop is performed on the following condition: Strength of 600 mg, only 1 excipient will be added and no diluents will be added. The percentage of disintegrant to be added was determined by the result of the Eq. (5). It is added the fixed formula of lubricants recommended by the expert system.

The selected formulas (detailed in Table 9) were prepared following the next steps:

- Weighing all the raw material except lubricants.
- Weighing the lubricants (this mixture is not added at this moment).
- Pass the mixture of API + disintegrant without excipients through a 600 μm sieve.
- Mix the mixture of API + disintegrant without excipients using a Turbula® mixer for 10 min.
- Add the lubricants and mix again for 2 more minutes.
- The eight proposed formulations were compressed in a Bonals® (Cornellá de Llobregat, Spain) continuous eccentric press, provided with 19 × 10 mm punches.

2.6. Method of characterization of Ibuprophen 600 mg ODT tablets

2.6.1. Disintegration

This disintegration test is carried out according to USP method, with disk and without disk. PharmaTest PTZ® equipment was used.

The acceptance criterion is that tablets must be disintegrated in $T \leqslant 3$ min. [24,25].

Table 6
Test results of eight disintegrants characterized by the SeDeM-ODT expert system divided in parameters and factors and IGCB. In the last column, it is showed the IGC index obtained with the original SeDeM expert system.

Excipient	Parameters (radius)												FACTOR						
	Da	Dc	Ie	IC	Icd	IH	α	t″	%HR	%H	%pf	(IO)	DE	DCD	DSD	Dim.	Comp	Flow/ P.Flow	Lubr/ Stab.	Dosage/ Lubricity	Disgregability	IGCB
AQUASORB A500®.	4.46	6.33	5.50	5.89	7.24	5.27	0.00	0.00	3.14	2.16	8.38	9.95	0.0	0.0	0.0	5.40	6.21	1.76	2.65	9.16	0.0	3.78
Brenncel-DIS®	9.26	10.00	1.67	3.70	0.46	5.91	0.00	3.45	2.90	10.00	9.80	4.60	0.0	0.0	0.0	9.63	1.94	3.12	6.45	7.20	0.0	4.00
Glycolys ®	8.94	9.81	0.83	1.79	0.32	6.34	0.00	9.42	4.31	2.08	0.00	10.00	7.80	9.00	8.77	9.38	0.98	5.25	3.19	5.00	8.52	5.14
Nymcel ZSB10®	3.80	5.89	7.82	7.12	7.53	4.82	0.00	0.00	1.60	2.79	0.00	10.00	5.76	6.63	4.90	4.84	7.49	1.61	2.19	5.00	5.76	4.44
Nymcel ZSD16®	5.00	7.26	5.19	6.23	10.00	5.16	0.00	0.00	4.42	4.71	0.00	10.00	0.00	0.00	0.00	6.13	7.14	1.72	4.57	5.00	0.00	3.75
Pharmaburst C1 ®	4.50	5.62	3.69	3.99	10.00	5.84	6.49	7.25	5.70	6.72	6.20	3.65	9.66	9.73	9.57	5.06	5.89	6.53	6.21	4.93	9.65	6.38
Polyplasdone XL10®	3.85	5.21	5.67	5.23	10.00	5.49	10.0	0.00	5.30	0.00	0.00	10.00	2.34	7.50	6.63	4.53	6.97	5.16	2.65	5.00	5.49	5.00
Polyplasdone XL®	3.02	3.95	6.49	4.70	8.05	5.64	0.00	8.34	5.00	0.00	6.50	2.75	8.00	9.40	9.10	3.48	6.41	4.66	2.50	4.63	8.83	5.57

Table 7
Evaluation of compressibility factor: Amount of excipient required (CP%) to ensure that mixture with Ibuprophen will give an IGBC of 5 (in bold% of excipient chosen to be added).

	AQUASORB A500®	BRENNCEL-DIS®	GLYCOLYS®	NYMCEL ZSD-16®	NYMCEL ZSB-10®	POLIPLASDONE XL®	POLIPLASDONE XL-10®	PHARMABUST C1®
RE	6.21	1.94	0.98	7.14	7.49	6.41	6.97	5.89
RP	4.46	4.46	4.46	4.46	4.46	4.46	4.46	4.46
R	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
CP*	30.86	−21.43	−15.52	20.15	17.82	27.69	21.51	37.76

Table 8
Evaluation of dimension factor: Amount of excipient required (CP%) to ensure that mixture with Ibuprophen will give an IGBC of 5 (in bold% of excipient chosen to be added).

	AQUASORB A500®	BRENNCEL-DIS®	GLYCOLYS®	NYMCEL ZSD-16®	NYMCEL ZSB-10®	POLIPLASDONE XL®	POLIPLASDONE XL-10®	PHARMABUST C1®
RE	5.4	9.63	9.38	6.13	4.84	3.48	4.53	5.06
RP	3.39	3.39	3.39	3.39	3.39	3.39	3.39	3.39
R	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
CP*	80.10	25.80	26.88	58.76	88.97	−1588.89	58.77	96.41

2.6.2. Dissolution profile

It was carried out according to USP method [26–27] taking samples at the following times: 1 min, 2 min, 3 min, 4 min, 5 min, 15 min, 30 min, and 60 min. This test was performed using USP-II equipment: Sotax AT7 Smart® with autosampling device at the following conditions:

- Dissolution media. Buffer solution (KH_2PO_4) (pH 7.2).
- T^a 37 °C ± 0.5 °C.
- Speed: 50 rpm.
- Volume of media in each vessel: 900 mL.
- Time: 60 min.

Each sample taken (5 mL) at the specified time is diluted to 250 mL with buffer solution, and then, it is filtered and read in a spectrophotometer at 221 nm.

2.6.3. Preparation of standard

The standard was prepared by weighing 66.67 mg of Ibuprophen (standard) and diluting with buffer solution to 500 ml, then dilution 1:10 [25].

2.6.4. Acceptance criteria

A formulation will be considered an ODT tablet, if $Q \geqslant 80\%$ in 3 min and $Q \geqslant 100\%$ in 5 min (Q = percentage of dissolution), according to the authors.

2.6.5. Hardness

It is performed according to USP [28] and Ph Eur ⟨2.9.8⟩ [29], using Erweka TBH30 equipment.

2.6.6. Friability

It is performed according to USP [30] and Ph Eur ⟨2.9.7⟩ [31] using Erweka TA10 equipment. It was evaluated if weight variation was $\leqslant 1\%$.

3. Results and discussion

3.1. Characterization of the disintegrants using new expert system SeDeM-ODT

The Ibuprophen was characterized with SeDeM expert system (Table 5), and it was found that two parameters must be improved: dimension and compressibility, since they are below to 5. It was not decided to improve the factor flowability/powder flow, since it is expected that this factor will increase when the standardized formula of lubricant is added to the formulations.

The results corresponding to the determination of the IGCB using SeDeM-ODT expert system for the eight excipients are detailed in Table 6, where it is shown that four disintegrants (Glycolys®, Pharmaburst C1®, Polyplasdone XL10®, and Polyplasdone XL®) have an IGCB $\geqslant 5$. Therefore, they can be used in a high percentage in combination with the API model (Ibuprophen) to obtain ODT by direct compression.

Disgregant Aquasorb A500®: According to Table 6 and Fig. 3, it is observed that Aquasorb A500® has reduced the IGC = 4.63 to IGCB = 3.78, so it is not recommended to be used in order to obtain ODT of Ibuprophen 600 mg. It was an expected result, since SeDeM-ODT model predicts formulations that are able to produce tablets by direct compression and able to disperse in few minutes. In this specific case, the method was not recommended to compress the mix since bucodispersibility factor is zero. To prove this prediction of the ODT-SeDeM, the mix will be compressed and analyzed.

Disgregant Brenncel-Dis®: According to Table 6 and Fig. 4, it is observed that Brenncel-Dis® has an IGCB = 4.00, which was reduced in comparison with IGC = 4.90. Therefore, it is not recommended to be used to obtain ODT of Ibuprophen 600 mg. Nevertheless, the formulation allows the obtention of tablets, as IGC is near to 5, although they will not have the bucodispersibility properties that are intended in this study. To prove this prediction of the ODT-SeDeM, the mix will be compressed and analyzed.

Disgregant Glycolys®: According to Table 6 and Fig. 5, it is observed that Glycolys® has an acceptable IGCB (5.14), in front of IGC (4.27), but if Table 6 is analyzed in detail, then it is noted that the Cohesivity Index is very low, which could explain the good disgregability properties due to this low cohesion of particles. In addition, a low compressibility index could indicate that tablets will have a low friability, and there is a potential risk to obtain broken or capped tablets during the compression process. This lower value corresponding to Compressibility of Glycolys® could be due to the spherical particles, which can impact directly on the plasticity properties observed during the experimental characterization. This could be supported with a high value corresponding to parameter dimension [32–35].

Disgregant Nymcel ZSB-10®: According to Table 6 and Fig. 6, it is observed that Nymcel ZSB-10® has an IGCB very near to 5 (IGCB = 4.44), which was increased compared with IGC (4.08), but it does not comply with the requirements IGCB $\geqslant 5$. Even though when data in Table 6 are analyzed in detail, it is observed that disgregability properties are higher than 5 (5.76), Cohesivity

Table 9
Formulas of bucodispersable tablets (ODT) of Ibuprophen 600 mg calculated for a batch of 400 g of mixture.

Disintegrant	Batch size = 400.00 g					Theoretical weight of the tablet (mg)	IGBC	Factor to be improved
	API(g)	EXCIPIENT(g)	TALC(g)	AEROSIL(g)	Mg-STEARATE (g)			
AQUASORB A500 ®	262.56	123.44	9.44	0.56	4.00	914.08	4.63	Compressibility
NYMCEL ZSD-16®	305.40	80.6	9.44	0.56	4.00	785.85	3.75	
NYMCEL ZSB-10®	314.72	71.28	9.44	0.56	4.00	762.58	4.44	
POLIPLASDONE XL®	275.24	110.76	9.44	0.56	4.00	871.97	5.57	
POLIPLASDONE XL-10®	299.96	86.04	9.44	0.56	4.00	800.11	5.00	
PHARMABUST C1®	234.96	151.04	9.44	0.56	4.00	1021.45	6.38	
BRENNCEL-DIS®	282.8	103.2	9.44	0.56	4.00	848.66	4.00	Dimension
GLYCOLYS®	278.48	107.52	9.44	0.56	4.00	861.82	5.14	

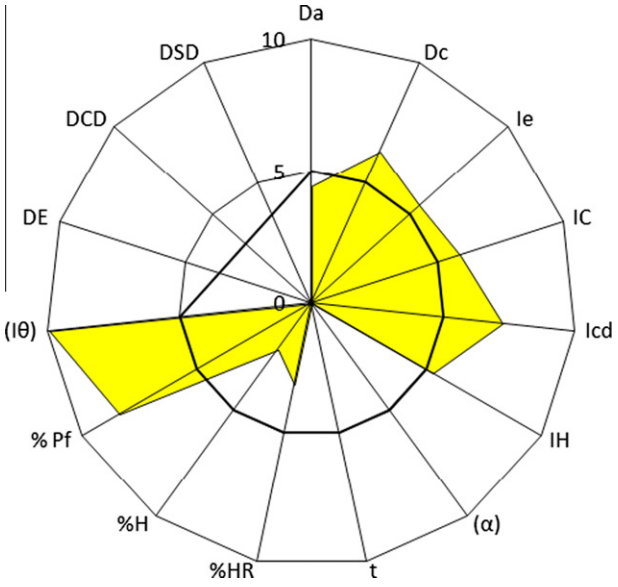

Fig. 3. Diagram SeDeM-ODT of Aquasorb A500® (IGCB = 3.78). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

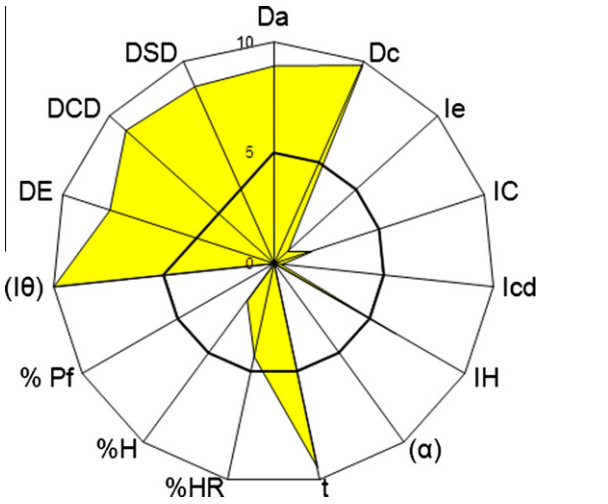

Fig. 5. Diagram SeDeM-ODT for Glycolys® (IGCB = 5.14). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

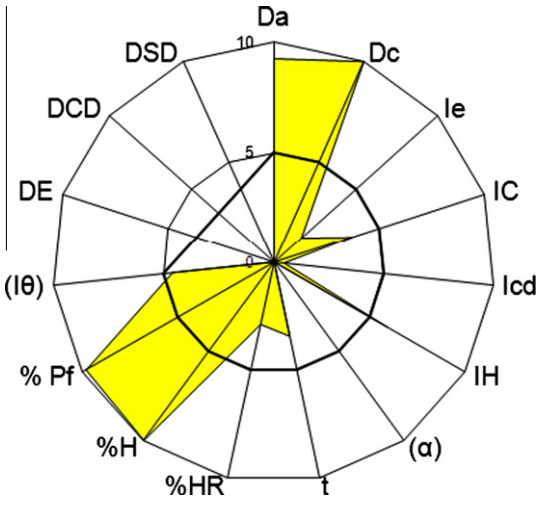

Fig. 4. Diagram SeDeM-ODT for Brenncel-DIS® (IGCB = 4.00). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

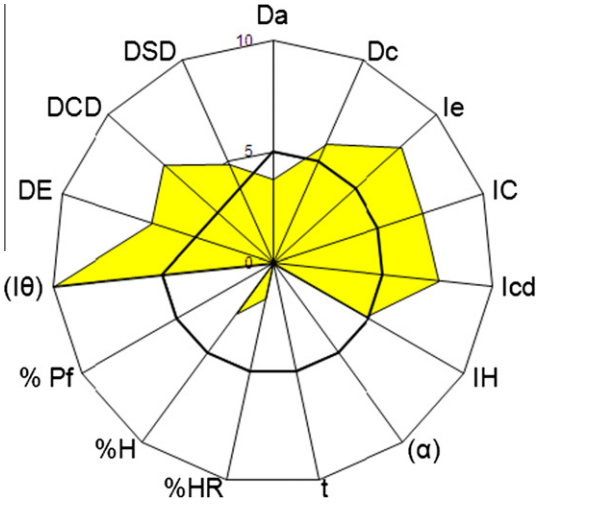

Fig. 6. Diagram SeDeM-ODT for Nymcel ZSB-10® (IGCB = 4.44). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Index is high (7.54), and compressibility factor is also higher (7.49), but it is required to improve parameters such as flowability/powder flow and lubricity/stability, and probably it could be enhanced with the combination of Ibuprophen and the standardized formula of lubricants. Then, Nymcel ZSB-10® must not be

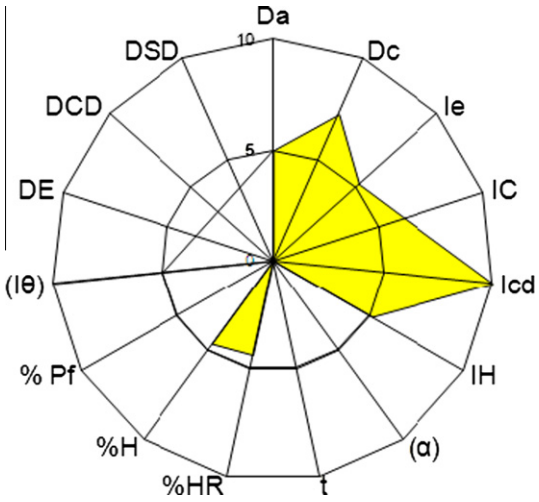

Fig. 7. Diagram SeDeM-ODT for Nymcel ZSD-16® (IGCB = 3.75). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

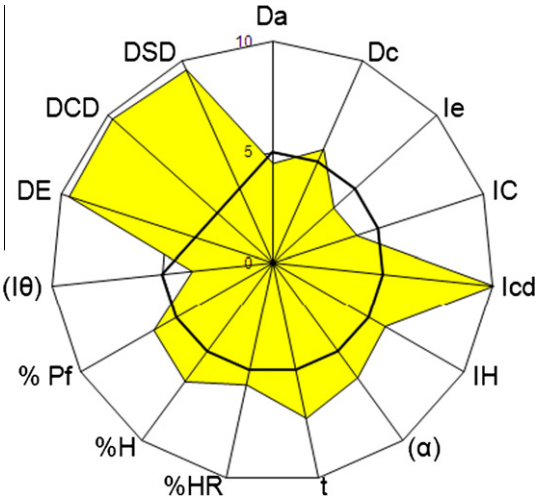

Fig. 8. Diagram SeDeM-ODT for Pharmaburst C1® (IGCB = 6.38). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

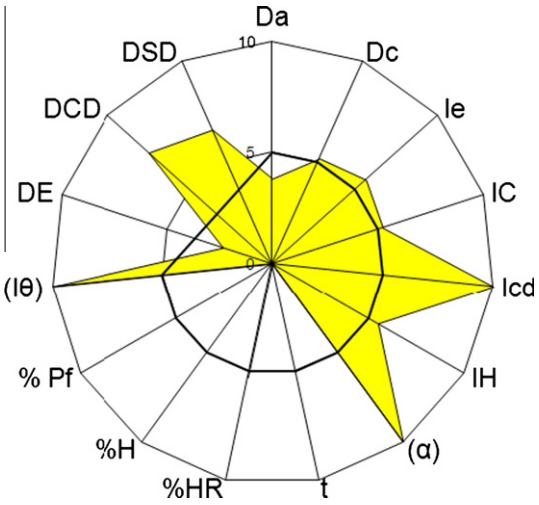

Fig. 9. Diagram SeDeM-ODT for Polyplasdone XL-10® (IGCB = 5.00). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

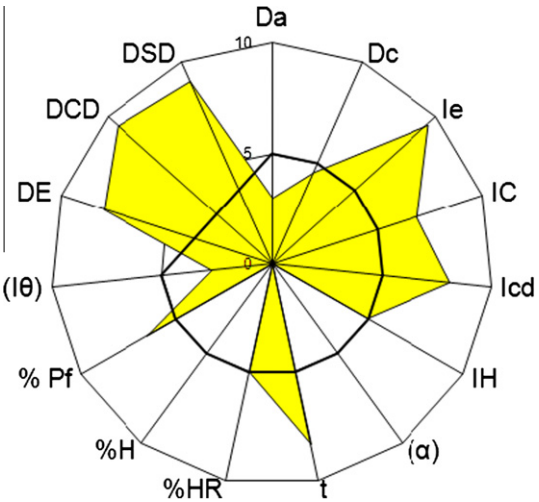

Fig. 10. Diagram SeDeM-ODT for Polyplasdone XL® (IGCB = 5.57). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

discarded, since it is an excellent option when the gaps will be covered with the standardized formulas of lubricants. Therefore, it is decided to use Nymcel ZSB-10® to perform the study along with the other four disintegrants.

Disgregant Nymcel ZSD-16®: According to Table 6 and Fig. 7, it is observed that Nymcel ZSD-16® has an IGCB lower than 5 (IGCB = 3.75), and it is lower than the previous IGC = 4.60, which was produced due to the poor valor of the disgregability parameter for this excipient (it was 0). Therefore, the SeDeM-ODT expert system does not recommend using at a high percentage this excipient to obtain Ibuprophen 600 mg ODT tablets.

Disgregant Pharmaburst C1®: According to Table 6 and Fig. 8, it is observed that Pharmaburst C1® has an acceptable IGCB (6.38), which is higher than the previous IGC (5.52), which was produced because the disgregability factor for this excipient has been higher than 5. Therefore, it can be used in a higher percentage to obtain Ibuprophen 600 mg ODT tablets. In general, all the parameters are good, including disgregability, which is very high because Pharmaburst C1® is a coprocessed excipient with improved disintegrating properties.

Disgregant Polyplasdone XL-10®: According to Table 6 and Fig. 9, it is observed that Polyplasdone XL-10® has an IGCB = 5.00, which was increased compared with IGC = 4.32 due to a good disgregability factor of this disintegrant. Therefore, it can be used in a higher percentage to obtain Ibuprophen 600 mg ODT tablets.

Disgregant Polyplasdone XL®: According to Table 6 and Fig. 10, it is observed that Polyplasdone XL® has an IGCB = 5.57 compared to IGC = 4.82, which was produced by the disgregability parameter (8.83) and Cohesivity Index (8.05), both of them very high. Then, it is concluded that it can be used in a higher percentage to obtain Ibuprophen 600 mg ODT tablets.

3.2. Design of ODT formulations

Table 6 shows the results of the SeDeM and SeDeM-ODT for 8 disintegrants according to the six specified factors: dimension, compressibility, flowability/powder flow, lubricity/stability, lubricity/dosage, and disgregability.

The model drug analyzed here, i.e., ibuprophen (Table 5), has a compressibility index lower than 5 (IGC = 4.48), which means that

Table 10
Characterization of the ODT formulations.

	Formulation with AQUASORB A-500®	Formulation with BRENNCEL-DIS®	Formulation with GLYCOLYS®	Formulation with NYMCEL ZSB-10®	Formulation with NYMCEL ZSD-16®	Formulation with POLYPL XL-10®	Formulation with PHARMABUST C1®	Formulation with POLYPL XL®
Disintegration time with disk (DCD)	>30	>30	0.48	0.43	1.78	>30	0.26	0.24
Disintegration time without disk (DSD)	>30	>30	0.63	0.52	3.26	>30	0.63	0.37
Friability (%)	0.00	0.72	40.55	0.43	0.27	0.60	0.27	0.66
Hardness (N)	52	81	48	52	78	77	59	45

to achieve an IGC $\geqslant$ 5, two factors of SeDeM characterization must be improved in order to obtain a 600 mg tablet. These factors are the dimension (3.39) and compressibility (4.46). For two of the other factors (lubricity/stability: 7.40; lubricity/dosage: 7.93), ibuprophen 600 mg has a good index, although its flowability/powder flow factor again has a value below 5 (1.90); this can be improved with the standardized formula of lubricants. Indeed, the SeDeM method provides a standardized formula of lubricants (accounting for 3.5% of the final formula) in order to improve directly this factor in the final formulation.

Eq. (5) was applied to the 8 disintegrants analyzed in combination with ibuprophen. The formula was applied twice, in order to evaluate, respectively, the compressibility and dimension factors. The results for improved compressibility are shown in Table 7, while those for the improved dimension factor are given in Table 8.

In Table 7, it can be seen that six excipients (marked in bold) could be selected to improve the compressibility factor, since around 30% (CP value) of the excipient would be needed. In this case, the therapeutic dose of ibuprophen would be between 200 mg and 600 mg (600 mg being the target here), therefore avoiding the production of large tablets. The excipients that improved factor compressibility in combination with ibuprophen were Aquasorb® A500, Nymcel® ZSD-16, Nymcel® ZSB-10, Pharmabust® C, Polyplasdone® XL-10, and Polyplasdone® XL.

The excipients with negative CP values were discarded, because they cannot be amended through the SeDeM expert system. This is because a negative value means that the excipient has a lower radius parameter value than the API, and therefore, the excipient makes the formulation less suitable for DC. It is thus impossible to formulate directly with only this excipient in the formulation.

As regards the dimension factor, Table 8 shows that there are two excipients (marked in bold) that fulfill the requirement of a CP $\leqslant$ 30% (It was not recommended a percentage upper than 30%, since it could result tablets too big). They are Brenncel-Dis® and Glycolys®.

The above eight (6 + 2) excipients were selected because, according to the SeDeM model, they improve the compressibility and dimension factors of ibuprophen, making the powder mixture suitable for obtaining tablets by DC. The composition of the eight formulas prepared in the laboratory is summarized in Table 9. The quantities shown in Table 9 were calculated as follows. The batch size was defined as 400 g, the weight of the disintegrant to be added was then calculated according to the percentage defined by SeDeM methodology (result from Table 7 or Table 8), a 3.5% of the batch weight corresponds to the lubricant formula, and the remaining percentage is made up of ibuprophen.

To validate the prediction of the SeDeM system, the eight formulations were prepared in the laboratory, and the mixture (excipient + API) was characterized again using the original SeDeM expert system and the new SeDeM-ODT model. Table 9 shows the formulas proposed by the SeDeM method.

3.3. Compression of Ibuprophen 600 mg orodispersible tablets

All the 8 formulas predicted by the SeDeM expert system were compressed without any problem in the process. Now, when the analysis of disgregability will be carried out, it could be checked whether the new expert system makes discrimination in the formulas to select only those suitable to become ODT tablets.

3.4. Characterization of the Ibuprophen 600 mg ODT designed by the SeDeM-ODT expert system

3.4.1. Disintegration

The disintegration time test of Ibuprophen 600 mg tablets was performed with disk and without disk, and it is detailed in Table 10, which indicates the formulations containing Glycolys®, Nymcel ZSB 10®, Pharmaburst C1®, Polyplasdone XL® that could be used like ODT since they show a disintegration time below than 3 min.

According to Table 6, it can be noted that SeDeM-ODT expert system recommended very efficient excipients including Nymcel ZSB 10® and exceptuating Polyplasdone XL-10®. This result was the expected, since Polyplasdone XL-10® was used in a percentage of 21.5% in the formulation. This results indicate that additional trials are required increasing the quantity of this disintegrants to obtain Ibuprophen 600 mg ODT, since it was observed during the execution of the test that formulation containing Polyplasdone XL-10® captured water by swelling mechanism. Then, the disintegration processes started and the tablets break into two parts, but it was not observed a complete disintegration. This could be due to Polyplasdone XL-10® as it has a smaller particle size compared to Polyplasdone XL® in which the swelling is produced and it becomes difficult for the entrance of water. In addition, the formulation containing Polyplasdone XL-10® has less percentage of disintegrants than Polyplasdone XL® (formulation?).

3.4.2. Friability

The results of friability are detailed in Table 10, and it can be noted that several formulations are suitable, but formulation containing Glycolys® has a higher percentage of friability. This result was the expected, since during the characterization of the formulation by SeDeM-ODT expert system, it was noted that formulation containing Glycolys® had a low Cohesivity Index. Thus, this formula is not recommended to be used in the development of ODT.

3.4.3. Hardness

When hardness was performed on the eight formulations (Table 10), it was observed that formulation of Ibuprophen containing disintegrants up to 10% has not high hardness value, and only three formulations containing Brenncel DIS®, Nymcel ZSD 16® and Pharmaburst C1® have a hardness value near to 80 N, which indicates that packaging could be used without special requirements.

Table 11
Dissolution profile test of the eight formulations developed and tested.

Formula	% 1 min	% 2 min	% 3 min	% 4 min	% 5 min	% 15 min	% 30 min	% 60 min
AQUASORB A500® + Ibuprophen + Lubric.	1.94	3.56	4.84	4.95	6.20	11.74	12.17	18.16
Brenncel-DIS® + Ibuprophen + Lubric.	0.69	0.95	1.36	1.41	1.70	3.55	6.36	11.37
Glycolys ® + Ibuprophen + Lubric.	5.11	19.46	37.89	56.63	75.43	102.96	102.59	105.30
Nymcel ZSB10® + Ibuprophen + Lubric	30.31	66.92	85.57	93.31	97.19	100.00	100.74	101.28
Nymcel ZSD16® + Ibuprophen + Lubric	17.24	44.40	73.06	86.17	95.18	99.37	98.96	99.39
Pharmabust C1 + ® + Ibuprophen + Lubric	16.97	40.45	76.04	101.29	100.91	101.81	101.01	100.94
Polyplasdone XL10® + Ibuprophen + Lubric	3.35	6.09	9.18	13.59	17.59	47.26	57.59	78.50
Polyplasdone XL® + Ibuprophen + Lubric	27.02	50.26	70.33	82.15	92.06	101.61	102.42	102.17

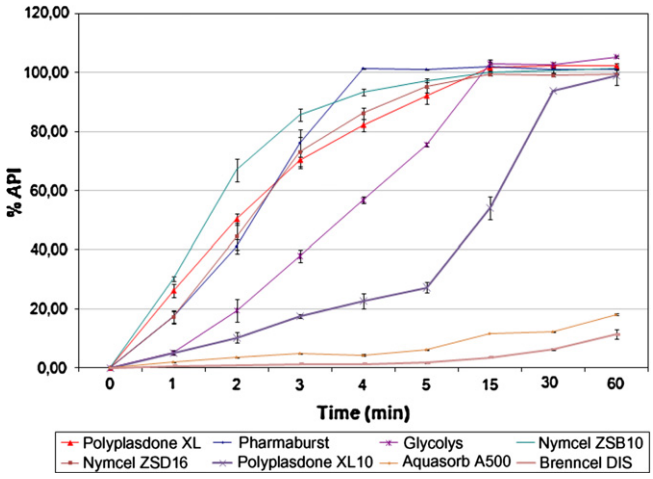

Fig. 11. Dissolution profile of the 8 formulations of Ibuprophen ODT 600 mg developed with the expert system SeDeM-ODT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4.4. Dissolution profile

The dissolution test is not specific for ODT, since the Eur Ph indicated that the only requirements are given for the disintegration time ($\geqslant$3 min) [25]. The dissolution test of these formulations was performed according to USP [27], in order to determine whether Ibuprophen 600 mg ODT dissolves $Q \geqslant 80\%$ in 60 min (Table 11 and Fig. 11).

When Fig. 11 and Table 11 are analyzed, it is observed that the formulations containing Glycolys®, Nymcel ZSB 10®, Pharmaburst C1® and Polyplasdone XL® meet this requirement (all dissolve between 4 and 15 min), but only Nymcel ZSB-10® meets exactly the authors requirement of $Q > 80\%$ in 3 min.

3.4.5. Discussion of results

As the SeDeM-ODT predicted, the characterization of Ibuprophen 600 mg Orodispersible Tablets containing Aquasorb A500® (30.86%) and Brenncel DIS® (25.80%) showed problems to accomplish disintegration time according to SeDeM-ODT prediction (IGCB = 3.78, for Aquasorb A500® and IGCB = 4.00 for Brenncel DIS®). Both were formulated at the laboratory, and tablets were obtained by direct compression. However, both could not accomplish with the disintegration requirement of an ODT tablet. No dissolution test was performed with these tablets, so it has been proved that the prediction was right when there is no suitability for disaggregation properties in a mixture.

In the preparation of Ibuprophen 600 mg ODT using Glycolis®, tablets that are expected to be ODT were obtained, since Glycolis® has IGCB = 5.14. In fact, the results of this formulation are acceptable except for friability and hardness test. Then, it is also found that the use of a high percentage of Glycolis® could provide acceptable results of disintegration and moderate results for dissolution.

Orodispersible tablets of Ibuprohen containing Nymcel ZSB10® were obtained at the laboratory, but it was noted that the initial formulation had and IGCB = 4.44. Nevertheless, it was selected and considered an exception, since factor disgregability (5) and test Cohesivity (7.53) Index were adequate. Therefore, it is expected that this excipient could be used in a high percentage, and the tablets will have ODT properties.

In the preparation of Ibuprophen 600 mg orodispersible tablets using Nymcel ZSD16®, it was noted that mixture had an IGCB = 3.75. Therefore, it was expected that the tablets could not be used like ODT, since the SeDeM-ODT expert system is informing about not adequate disintegrating properties, which was confirmed in the laboratory test.

In the preparation of Ibuprophen 600 mg ODT using Pharmaburst C1®, it was successfully compressed at the laboratory by direct compression, and it is expected that it has ODT properties, since SeDeM-ODT expert system indicates that this is possible because the final mixture had an IGCB = 6.38. Using this excipient, the formulation obtained shows the highest IGCB among the eight formulations.

During the preparation of Ibuprophen 600 mg ODT using Poliplasdone XL10®, it was noted that it is possible to obtain tablets by direct compression that will have ODT properties, since the final mixture had an IGCB = 5.00.

During the preparation of Ibuprophen 600 mg ODT using Poliplasdone XL®, it was observed that it is possible to obtain tablets by direct compression with ODT properties, since it had an IGCB = 5.57.

From the previous results and discussion, it can be said that the SeDeM_ODT expert system seems to be really helpful, as this tool informs about those formulations which will be unacceptable, thus reducing the lead-time of ODT development. SeDeM-ODT expert system is a preformulation and formulation tool for ODT, which was proved to be useful, effective, trustworthy, and reproducible to develop ODT in an easier and faster way, and the obtained tablets are effective, since the SeDeM-ODT expert system evaluates the specific properties of these kinds of tablets.

SeDeM-ODT expert system informs about the disintegration capacity of excipients to be used in direct compression, thus permitting obtaining tablets with bucodispersibility characteristics. SeDeM-ODT expert system permits to obtain ODT by direct compression using only 1 excipient (1 disintegrant) in the formulation along with the standardized mixture of lubricants and the API.

It was proved that disintegrants with a factor disgregability greater than 5 have an impact on IGCB in a positive way. So, the strategy to design ODT exposed in Fig. 2 is effective.

When some disintegrants are used in a higher percentage, the tablets produced have opposed characteristics to those expected. Therefore, SeDeM-ODT expert system only recommends those that increase disgregability and avoid those that produce the opposite effect. So, unnecessary trial formulations are avoided when SeDeM-ODT expert system is used, thus reducing the lead-time of ODT development.

The SeDeM expert system has been improved, creating a new innovator tool for preformulation studies of orodispersible tablets obtained by direct compression technology. Therefore, it could be concluded that SeDeM-ODT expert system in comparison with SeDeM expert system is more efficient to select eight formulations, since it was demonstrated that SeDeM-ODT expert system recommend only those with good bucodispersibility properties (6 formulas) and did not recommended to produce the eight formulations. Therefore, it is demonstrated that the new SeDeM-ODT expert system facilitates the selection of excipients that will provide ODT by direct compression technologies.

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