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Design of *Peumus boldus* tablets by direct compression using a novel dry plant extract

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Abstract

A solid pharmaceutical dosage formulation using a novel dry plant extract of *Peumus boldus* MOL. (Monimiaceae) (Pb) is proposed. The botanical evaluation of plant material, through morphological and anatomical diagnosis, is presented. This evaluation permits to identify the herb to be used correctly. The analysis of the most extractive solvent mixture and the attainment of plant extract (fluid and dry) are reported. Several formulations (tablets) containing a novel dry plant extract of Pb and common excipients for direct compression are evaluated. The following formulation: dry plant extract of Pb (170 mg), Avicel PH101 (112 mg), Lactose CD (112) and magnesium stearate (6 mg), compressed at 1000 mPa, showed the best pharmaceutical performance.

Keywords: Dry plant extract; Direct compression; *Peumus boldus* MOL.; Tablets

1. Introduction

Currently, an increased use of 'traditional medicine' is observed in developed and developing countries (WHO Information 1996; Akerele 1991). This kind of therapeutic strategy is essentially based on the use of herbal medicines or 'phytomedicines'.

Owing to this, legal standards of quality control about these products have been enacted in several countries including Argentina. Consequently, a set of regulations regarding all process involved in phytomedicine attainment (design, formulation and production) was established in order to fulfil with requirements of quality, safety and efficacy. Therefore, it is essential, on one hand, to establish the botanical, chemical and sanitary control of the plant material to be used and, on the other, a suitable design of the formulation and evaluation of its pharmaceutical properties; this latter guarantees the therapeutic efficacy. The design and formulation of tablets using dry plant extract

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(DPE) as active material have several technical drawbacks that conspire against the quality of the product. Generally, DPE has 'poor' rheological properties and the compactability to be used in direct compression (DC) technology.

In this work, the design of a phytomedicine using a novel DPE 'boldo' is proposed. Boldo consists of the dried leaves of *Peumus boldus* MOL. (Monimiaceae). This herb possesses faintly aromatic taste and somewhat unpleasant pungent odour, reminiscent of thymol, bitter and slightly astringent (British Herbal Pharmacopoeia, 1996).

2. Materials and methods

2.1. Materials

Fumed silica (Cab-O-Sil), α-lactose monohydrate (Lactose), dicalcium phosphate dihydrate (Emcompress) and microcrystalline cellulose (Avicel PH101) were used. *P. boldus* (Pb) samples from commercial source (Sample 1) collected in Concepción, Chile (Sample 2, voucher specimen: Concepción, Jardín Botánico de la Universidad de Concepción, Barboza 126, I-1999), were selected as plant material. Distilled water and alcohol from commercial source (96°) were used. All reagents were of analytical grade.

2.2. Methods

2.2.1. Botanical analysis

For the anatomical analysis, fresh or fixed in Formalin-Aceto-Alcohol (5:5:90) leaves of *P. boldus* were used. Sections for study under light microscope were prepared after dehydrating the material in an ethyl alcohol/xylene series and then included in an embedding medium ('paraplast'). Sections were sliced 10-15 μm thick and stained with safranine–alcianblue–fast green combination (Conn et al., 1960). Stomata and trichomes were also analysed in surface view. Differential histochemical staining evidenced the different cellular contents (Sudan III for lipids, Dragendorff reagent for alkaloids).

Original drawings were made using a lucida camera. Microphotographs were photographed in an Axiophot microscope. The calcium oxalate was detected using Differential interferential contrast.

2.2.2. Solid Residue (SR) assay

The SR content of fluidextracts was determined by evaporation of the solvent under reduced pressure, and then dried in an oven (40 °C) to constant weight.

2.2.3. Density and compressibility assays

To determine the density of the samples, the powder was gently poured into 10 cm^3 graduate cylinder to a total volume of 10 cm^3. The bulk density (*DB*) was calculated as the ratio between weight (g) and volume (cm^3).

To determine the ultimate tap density (*DT*) the cylinder was tapped over 1.0 inch vertical drop, at 1 s interval, until no measurable change in volume was noticed. The compressibility of the powder was evaluated using the Hausner Ratio (*HR*) (Schmidt and Rubensdörfer, 1994) as shown in Eq. (1):

$$HR = \frac{DT}{DB} \quad (1)$$

2.2.4. Angle of repose (α)

The dynamic α for each mixture of powder was determined by the funnel method as described in the literature (Lantz and Schwartz, 1990).

2.2.5. Tablet compaction

The DPE and excipients, except magnesium stearate, were blended for 12 min by tumbling, thus the corresponding amount of magnesium stearate was added and blended for another 4 min, and then compressed for 5 s at different compaction pressures in a hydraulic press provided with a manometer (Delfabro). Flat punches with a 13.0 mm diameter were used. The weight of each tablet was 400 mg. Tablet hardness was measured on recently prepared tablets with an AVIC hardness tester.

2.2.6. Disintegration test

The disintegration tests were performed at 37 °C in distilled water, using Hanson disintegrator, according to USP XXIII. Assays were made in triplicate.

2.2.7. Fluid (FPE) and dry (DPE) plant extract attainment

To obtain FPE, the herb was ground and macerated during 72 h in an extractive solution, and then filtered. DPE was obtained according to method previously described (Palma et al., 1999).

2.2.8. Quantitative determination of boldine

The quantitative analysis of boldine was then performed according to the Pharmacopoeia Helvetica Editio Setima, 1995, where potentiometric titers were changed into spectrophotometric measurements.

3. Results and discussion

It is well known that tablet manufacture through direct compression offers many advantages over other methods (Shangraw, 1990). However, when DPE is incorporated as an active component, it is necessary to bear in mind some considerations: (i) the quality of the plant material should be guaranteed from a botanical, chemical and sanitary point of view, (ii) the components of the formulation, like excipients and the active compounds, have to possess some characteristics referred mainly as flowability, compactability and compressibility, and (iii) the design of the formulation must satisfy pre-determined biopharmaceutical standars. For this study, *P. boldus* exhibiting choleretic, diuretic, stomachic and cholagogic properties (Newal et al., 1996) was selected.

The assays carried out to design tablets from PDE of Pb are (i) evaluation and control of plant material, (ii) achievement of fluid and dry extracts, and (iii) design and biopharmaceutical assesment of the formulations.

3.1. Evaluation and control of plant material

This aspect deals with a complete exomorphological and anatomical description of *P. boldus* in order to devise the diagnostic features that ensure the unequivocal identity of the species and the commercial samples (leaf) frequently used.

3.1.1. Exomorphology

Dioecious thermophilous small tree or shrub, 3–6 m high, with persistent and dense foliage. Young stems pubescent (trichomes non-glandular, simple, stiff, and stellate trichomes). Evergreen leaves, brevipetiolate, opposite, simple, elliptic or oval-elliptic, the blade 2.5–7 cm long, 2–4 cm wide, thick, coriaceous, brittle, upper surface rough and pellucid-punctated, entire and revolute margins (above all, the leaves from upper branches under full sun exposure), obtuse apex, equal and rounded based, dark green fresh leaves, drying paler, somewhat lighter below than above, venation brochidodromous (secondary veins not terminating at the margin but joined together in a series of prominent arches), the midvein impressed slightly to nearly flat above, prominent below, the 5-6 secondary vein pairs distinctly raised below, the tertiary veins slightly indistinct, both surfaces pubescent, aromatic, camphoraceous and pungent and bitter in taste. Axillary flowers or seldom terminal cymose inflorescences (5–12 flowered), relatively small (ca. 5 mm diam) and inconspicuous, greenish, imperfect, regular. Perianth cupulate, calyx pentamerous, corolla of 7–9 petals. Staminate flowers with ca. 25-40 stamens in 5–6 series, pubescent filaments provided with a pair of basilateral nectariferous appendages, and anthers opening by longitudinal slits. Pistillate flowers with many staminodia, gynoecium of 3–5 separate pubescent carpels with short style and elongated stigma; solitary, apical and pendulous ovule. Fruit of separate acuminate sweet drupes, collectively enclosed in the hypanthum, yellowish in colour. Seed with abundant, oily endosperm and small embryo; membranous episperm (Fig. 1).

3.1.2. Habitat and distribution

Endemic Chilean species from a very restricted area grows in sclerophyll forest and sbrublands from Coquimbo to Osorno up to 1200 m.s.m. (San Martín and Doll, 1998)

3.1.3. Diagnostic anatomical features

As from a pharmaceutical and medicinal point of view the *P. boldus* leaf is the vegetative organ exclusively used, the following anatomical de-

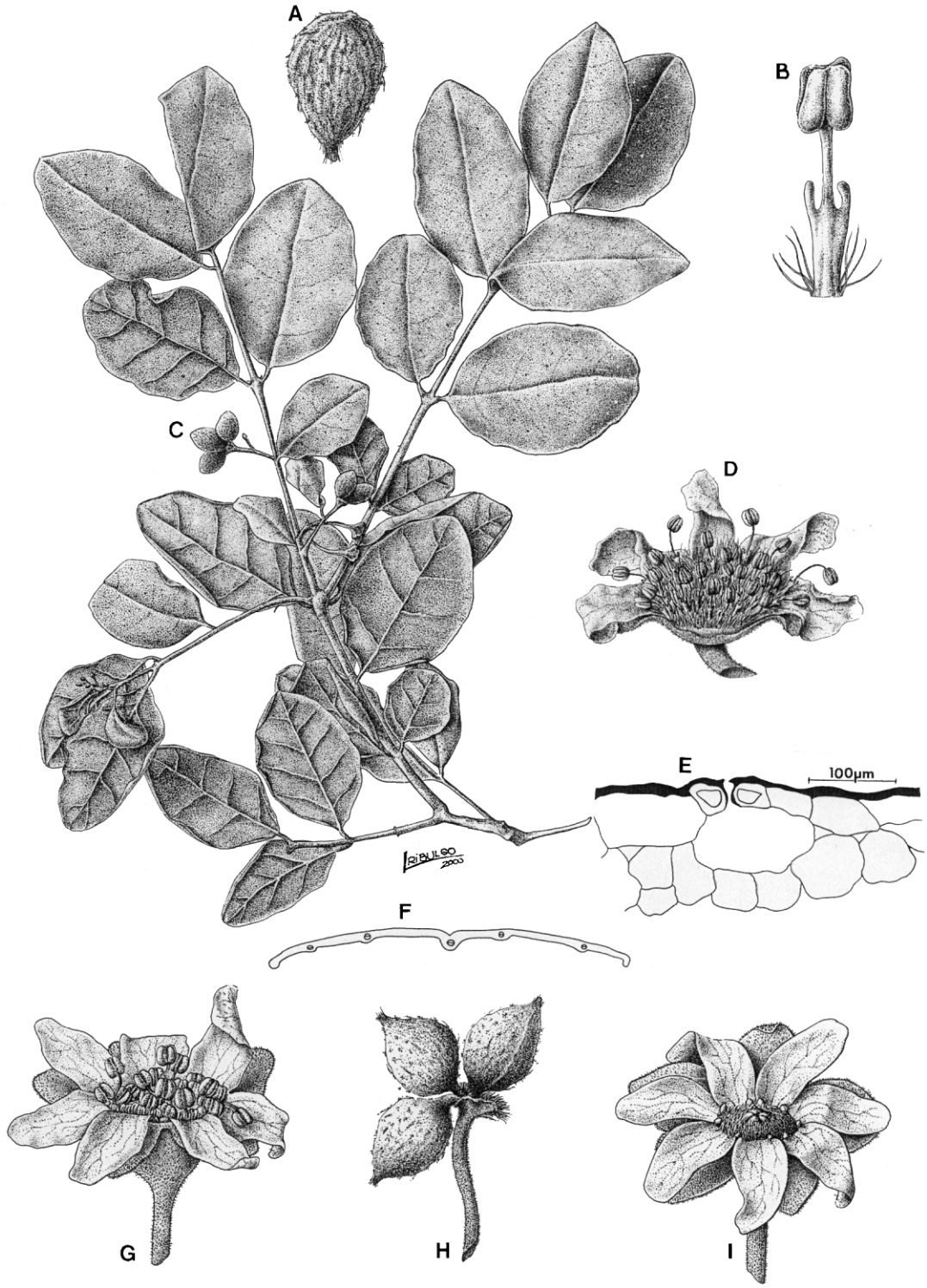

Fig. 1. *P. boldus* (Barboza 126). (A) drupe, × 45; (B) stamen and staminodes, × 18; (C) fruiting branch, × 1; (D) staminate flower cut lengthwise, × 7; (E) stoma in cross section; (F) leaf outline, in cross section, × 8; (G) staminate flower, × 7; (H) fruit enclosed in the hypanthium, × 4; pistillate flower, × 7.

scription includes only the most relevant features of this organ (Fig. 2).

a) Surface view: Upper epidermis is usually composed of polygonal cells with more or less straight walls; lower epidermis of sinuous thick walled cells with many noticeable pits. Stomata, confined to the lower epidermis (hypostomatic leaf), are usually anomocytic. Both surfaces covered equally by trichomes of two types: (1) Non-glandular trichomes, unicellular or two-armed from the base, each arm unicellular, and often with thickened walls, (2) Long isolated or tufted multicellular (up to 15-armed), sessile, thick-walled stellate trichomes on a sclerenchymatous base; the rays are multiangulated radiating outwards in all directions.

b) Cross section: Epidermis is usually composed of small cells, slightly thick and smooth cuticle. Abundant stomata with outer stomatal ledges, guard cells with chloroplast and sunken lower epidermis. Hypoderm consists of 3–5 collenchymatous layers beneath the upper dorsiventral mesophyll epidermis, including a single or, more rarely, two layers of palisade cells. Large intercellular spaces present in the 6–8-layered spongy tissue; large spherical secretory cells with yellow-

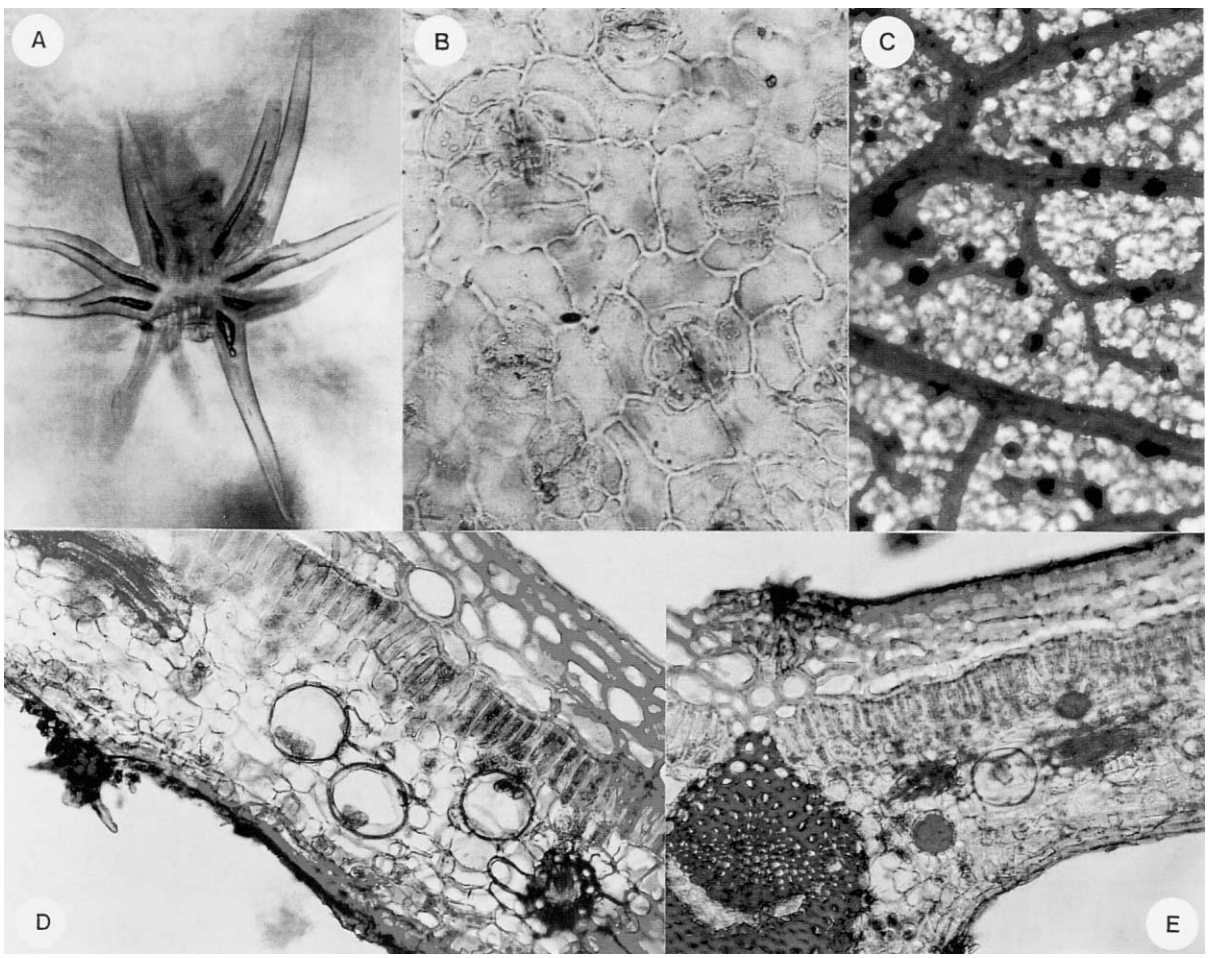

Fig. 2. Leaf anatomy of *P boldus* (Barboza 126). (A) stellate trichome (observe the thick-walled cells), × 200; (B) abaxial surface with anomocytic stomata, × 200; (C) surface view of the leaf showing adaxial surface without stomata, × 50; (D) mesophyll in cross section (observe the multiseriate hypoderm and the oil glands in the spongy tissue, × 200; (E) midvein in cross section, note the sclerenchymatous tissue around the vascular strand, × 200.

Table 1
Extractive strength of ethanol-water mixtures on *P. boldus* MOL.

Herb/solvent (g/100 ml)	Ethanol:water (Solvent)	Boldine/LPE (mg/100 ml)
24.95	100:0	66
25.05	70:30	99
25.09	60:40	90
25.02	50:50	82
25.02	40:60	73

ish oily content, frequently appearing as transparent dots in the leaf, generally situated in the mesophyll. Crystals chiefly in the form, of very numerous small needles of calcium oxalate, frequently present throughout the mesophyll; small cubical and prismatic crystals also found in the region of the veins. Vascular bundles of the larger veins usually surrounded by a large, well-developed sclerenchymatous sheath, and angular collenchyma below both epidermises.

3.2. Fluid and dry extracts attainment

The attainment of DPE from Pb was described in a previous work (Palma et al., 1999). This method is based on the adsorption of the solid residue of the plant contained in the corresponding liquid extract (LPE) on inert excipient (fumed silica).

To obtain this DPE it is necessary to know the amount of active component (boldine in this case) present in the herb and then determine which is the most efficient solvent system since it varies according to the species. In this case, we evaluate the extractive capacity of different ethanol:water mixtures. Results are shown in Table 1.

The solvent mixture ethanol:water (70:30) proved to be the most efficient/effective (in boldine concentration) to obtain LPE. This solvent system was also tested in the sample from Chile to get LPE. The LPE containing 0.99 mg/ml of boldine was used to develop a DPE according to the method previously described (Palma et al., 1999). The DPE containing 7.5% W/W of boldine was used to design and formulate the tablets. As shown in Table 2, the concentration of boldine in Sample 1 was lower than in Sample 2, this is due to that the fact that the former is a commercial sample whose lower quality could be more susceptible to adulteration.

3.3. Design and biopharmaceutical evaluation of the formulations

Dry powdered extracts do not currently exhibit the appropriate rheology and compressibility required to be processed by direct compression. Numerous reports have addressed techniques to solve this kind of problems, such as wet granulation with non-aqueous solvents, direct compression of spray dried extracts**,** and selection of suitable excipients for the formulation of dry plant extracts in direct compression tablets, and so on (Plazier-Vercamen and Bruwier, 1986; Díaz et al., 1996; Renoux et al., 1996). However, few studies have aimed at eliciting dry plant extracts of both good flowability and compactibility.

The rheological properties of DPE of Pb were assayed considering density, angle of repose and compressibility (Hausner Ratio, *HR*). Results are shown in Table 2.

These results are similar to those obtained from other species (Palma et al., 1999). The DPE possesses suitable rheological properties and compressibility, permitting its use in direct

Table 2
Rheological properties and compressibility of *P. boldus* DPE

Sample	Boldine (mg% *P*/*V*)	Solid residue (g% *P*/*V*)	Bulk density (*BD*)	Tap density (*TD*)	Angle of repose (°)	Hausner Ratio (HR)
1	53	5.27	0.263	0.4126	45	1.566
2	99	6.58	0.311	0.4736	36	1.489

Table 3
Composition of tablet formulations containing *P. boldus* MOL. DPE

Components	Formulation		
	1 (mg)	2 (mg)	3 (mg)
Pb DPE	170	170	170
Avicel PH101	–	112	112
Lactose CD	112	112	–
Emcompress	112	–	112
Mg stearate	6	6	6
Total weight	400	400	400

compression technology. Likewise, the evaluation of the influence of these extracts on the physical-mechanical properties of excipients like α-lactose monohydrate (Lactose CD), dicalcium phosphate dihydrate (Emcompress) and microcrystalline cellulose (Avicel PH101) showed that these properties are practically intact (Palma et al., 1999). Thereby, the design of the tablets using these three excipients at different rates and several compression forces was performed. The composition of the formulations is shown in Table 3.

The rheological properties, hardness and disintegration were evaluated in each formulation. The disintegration of tablets is taken, in this case, as biopharmaceutical parameters to evaluate comparatively the performance of the formulations, since boldine release from DPE is satisfactory (Palma et al., 1999). On the other hand, all formulations showed acceptable friability ($< 1\%$). Results are shown in Table 4.

The excipients selected, α-lactose monohydrate (Lactose CD) (Wade and Weller, 1994a), dicalcium phosphate dihydrate (Emcompress) (Wade and Weller, 1994b) and microcrystalline cellulose (Avicel PH101) (Wade and Weller, 1994c), possess defined physical-mechanical properties (Alderborn and Nyström, 1996) which may be transferred to the formulations according to the rates in which they occur.

As evidenced from Table 4, the higher densities of the powder mixture in formula 1 are due to the incorporation of Emcompress, which is a high density material. When this excipient is replaced by Avicel PH101 (formulation 2) or by Lactose CD (formulation 3), a significant reduction of density (BD as well TD) in the powder mixtures is observed.

With respect to compression behaviour, the influence of compression forces (CF) on the hardness and disintegration time of the compact is analysed (see Table 4).

When the CF is increased, as it can be expected, an increase of the hardness in the tablets is observed. This increase in hardness is more remarkable when formulations 2 and 3 are considered, because of the presence of Avicel PH101, which is a very compressible material.

About disintegration time, a faster one is observed when formulation 2 and 3 are assayed, owing to the incorporation of Avicel PH101. This excipient can produce the water uptake, swelling and quick rupture of the compact.

Table 4
Rheological and pharmaceutic properties of formulations containing *P. boldus* DPE

Formulation	*BD*	*TD*	*HR*	*α* (°)	Comp force (mPa)	Hardness (kg/cm^2)	Disintegration (min)
1	0.436	0.630	1.44	35	1000	3.34	8.51
					1500	3.84	17.36
					2000	4.64	20.92
2	0.409	0.595	1.45	30	1000	7.27	2.26
					1500	9.33	5.48
					2000	11.33	9.95
3	0.367	0.579	1.58	36	1000	6.98	2.84
					1500	8.53	4.90
					2000	10.1	7.86

In the same way, when the mixture of powder according to formulation 2 is compressed at 1000 kg/cm^2, tablets with the lowest disintegration time are obtained and, consequently, it could be selected as the most convenient from this point of view. Besides, this formula offers the advantage of minor spoil of the equipment due to the lower pressure of compression.

4. Conclusions

In the formulation of solid pharmaceutical dosage forms of DPE from of *P. boldus* MOL. (Monimiaceae), the main conclusions of the three aspects considered in this paper are: (i) the botanical evaluation of plant material permits to identify the species correctly. From a botanical viewpoint, the most relevant morpho-anatomical characters were: leaf with revolute margin, rough upper surface, pellucid-punctated (translucid oil glands), and with white protuberance of stellate trichomes on a sclerenchymatous base; stomata with outer ledges only in the lower surface, adaxial hypodermis, oil cells in the intercellular space of the spongy mesophyll, needles of calcium oxalate; (ii) the ethanol:water (70:30) mixture demonstrated better extractive efficiency. With this solvent system it was possible to achieve a FPE, which was then transformed into a DPE according to a previously described technique. The solid extract (DPE) exhibits suitable rheological, physical and mechanical properties, which make possible the design and tablet manufacture using direct compression technology; and (iii) the formulation containing dry plant extract of Pb (170 mg), Avicel PH101 (112 mg), Lactose CD (112) and magnesium stearate (6 mg), compressed at 1000 mPa, showed the best pharmaceutical performance.

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