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Research Article

Granulation by Roller Compaction and Enteric Coated Tablet Formulation of the Extract of the Seeds of *Glinus Lotoides* Loaded on Aeroperl® 300 Pharma

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Abstract. The purpose of this research was to improve the hygrpscopicity and poor flow properties of the crude dry extract of the seeds of *Glinus lotoides* and improve the disintegration time of the core-tablets for enteric coated formulation thereof. The liquid crude extract of the plant was adsorbed on granulated colloidal silicon dioxide (Aeroperl® 300 Pharma) at 30% *w*/*w* and the dry extract preparation (DEP) was dry-granulated with roller-compaction using Micro-Pactor®. Hygroscopicity, flow property and disintegration time were improved significantly due to the adsorption and granulation processes. Moreover, the DEP does not become mucilaginous even at higher relative humidity levels (above 65%). Oblong tablets (20×8.25 mm) containing 947 mg of the granulated DEP (equivalent to the traditional dose), 363 mg of Avicel® PH101 and 90 mg of Ac-di-Sol® as disintegrant were formulated using an instrumented eccentric tablet machine at 20 kN. The tablets showed a crushing strength of 195 N, a friability of 0.4% and disintegrated within 9 min. The tablets were then enteric coated using polymethacrylate co-polymers (Eudragit® L 100-55 and Kollicoat® MAE 100P). The coated tablets resisted disintegration or softening in simulated gastric fluid for a minimum of 2 h and disintegrated within 15 min in intestine simulated fluid at pH 6.8. In addition to controlling the release of the active agents, the enteric coating improved the strength and decreased friability of the core-tablets.

KEY WORDS: Aeroperl® 300 Pharma; dry granulation; enteric coated; *Glinus lotoides*; phytopharmaceutical.

INTRODUCTION

Glinus lotoides L. (Molluginaceae) is an annual or short-living perennial prostrate herb, (1) the seeds of which are traditionally used in Ethiopia as anthelminthics (2,3), and in India and Pakistan as antifungal and antitumor (4,5). The taenicidal activities against *Tenia saginata* and *Hymenolepis nana* worms (6–8), and the antitumor activities against Dalton's ascitic lymphoma in Swiss albino mice (5) have been evaluated. The pharmacological activities of the plant have been attributed to its saponins and flavonoids (2,3,5–8). Phytochemical investigation of *G. lotoides* afforded several hopane triterpenoidal saponins (glinusides A-I; lotoideside A-F and succulentoside B), flavonoids (vicenin-2; vitexin-2"-*O*-glucoside; apigenin-7-*O*-glucoside, isovitexin, and luteolin-7-*O*-glucoside) and isoflavonoids (9–13).

The crude extract of the seeds of *G. lotoides* showed poor flow properties and liquefied at relative humidity levels of 65% and above (14) indicating the challenges in tablet formulation of the dry extract. Dry plant extracts usually lack good flow properties to be processed by direct compression. In addition, because the active components of the extracts are diluted by co-extracted substances, high dosages are required. This is in conflict with the limited proportion in which the extracts can be incorporated into the final mixture for tablet compression (15). Numerous reports have addressed techniques used to solve these 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 (16–18). Preparation of a dry extract by adsorption of liquid plant extract on inert excipients, such as fumed silica, lactose, starch and dicalcium phosphate has been reported (19). The dry extract prepared with starch showed poor flow properties indicating the importance of proper selection of adsorbent (19).

In this work, liquid crude extract of the seeds of *G. lotoides* was adsorbed on granulated colloidal silicon dioxide (Aeroperl® 300 Pharma) to prepare dry extract suitable for enteric coated tablet formulation. Aeroperl® 300 Pharma, which has huge surface area and cavities for adsorption, has been effectively utilized as carrier for liquid and pasty active ingredients to convert them into free-flowing powders (20).

Enteric coating of tablets, capsules, granules, pellets, crystals and other drug-loaded cores serves to ensure their physical and chemical stability, to enhance patient compliance and to further improve their therapeutic efficacy. The enteric

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coating of *G. lotoides* tablets is justified for an immediate release of the active components in the small intestine, where they are used as anthelmintic agent as well as protection of the tablets for atmospheric humidity. The present study, therefore, reports on the preparation and physicochemical characterization of dry extract preparations (DEP) of the seeds of *G. lotoides* containing Aeroperl® 300 Pharma as inert sorption material, granulation using roller compaction and enteric coated tablet formulation of the DEP.

MATERIALS AND METHODS

Materials

Fruits of *G. lotoides* were purchased from the local market, 'Merkato' in Addis Ababa, Ethiopia. The identity was confirmed by the National Herbarium, Department of Biology, Faculty of Science, Addis Ababa University, Ethiopia (voucher specimen No. 003444). Hexane, methanol, n-butanol, diethyl ether, hydrochloric acid, potassium chloride, sodium chloride, sodium nitrite, potassium carbonate, magnesium chloride, ammonium nitrate and sodium tartarate dihydrate were all of pharmaceutical grade (Merck, Darmstadt, Germany). Formamide and Hydranal® composite 2 were obtained from Riedel-de Haën, Seelze, Germany.

The following excipients were used for preparation of dry extract, formulation of core-tablets and enteric coating: granulated colloidal silicon dioxide (Aeroperl® 300 Pharma, Degussa AG, Düsseldorf, Germany); microcrystalline cellulose (Avicel® PH 101 and PH 200, FMC Biopolymer, Hamburg, Germany); lactose cellulose granulate (Cellactose® 80, Meggle, Wasserburg, Germany); cross-linked sodium carboxy methyl cellulose (Ac-Di-Sol®, FMC Biopolymer); cross-linked polyvinyl pyrolidone (Kollidon® CL, BASF AG, Ludwigshafen, Germany); sodium starch glycolate (Explotab®, Mendell GmbH, Uetersen, Germany); magnesium stearate (Baerlocher GmbH, Munich, Germany); colloidal silicon dioxide (Aerosil® 200, Degussa AG); polymethacrylate copolymers (Eudragit® L 100-55, Röhm GmbH, Darmstadt, Germany and Kollicoat® MAE 100P, BASF AG); *i*-propanol; acetone (Fluka Chemie AG); 1,2-propylene glycol (BASF AG); acetyl tributyl citrate (CITROFOL® B II, Jungbunzlauer GmbH, Ladenburg, Germany); glycerol monostearate (Henkel KgaA, Düsseldorf, Germany); talc (Norwegian Talc GmbH, Bad Sonden-Salmünster, Germany); titan dioxide (Kronos Titan GmbH, Leverkusen, Germany); iron oxide (Sicovit Braun 70 E 172, BASF AG).

Methods

Dry Extract Preparation (DEP) of the Seeds of G. lotoides

Of defatted powder seeds of *G. lotoides*, 500 g were extracted with 5 L 60% MeOH in a 10-L beaker for 15 min using an Ultra-Turrax (Type T 45/N, IKA-Werk GmbH and Co., Janke & Kunkel, Staufen, Germany) at 10,000 rpm. The extract was filtered (filter press, A-20Z, Seitz-Werke GmbH, Bad Kreuznach, Germany) through filter sheets (T 1000, Pall Co., Bad Kreuznach, Germany) and concentrated using a rotavapor at 50 °C to a volume of 2-L. The amount of the dry extract in the concentrate was determined after drying a 10-mL sample in an oven and specified amount of granulated colloidal silicon dioxide (Aeroperl® 300 Pharma) was added. The mixture was further concentrated to a viscous mass and dried in a vacuum oven (VDL 53, Binder GmbH, Tuttlingen, Germany) at 40 °C and 125 mbar for 24 h. Various concentrations of Aeroperl® 300 Pharma (10, 20, 30, 40, 50 and 60% *w*/*w*) were utilized as an inert adsorbent to prepare the dry extract. The DEPs were pulverized in a ball-mill and passed through a sieve size of 250 μm. The physicochemical properties of the DEPs were characterized as described below.

Physicochemical Characterization of the DEPs

The particle size distribution of the DEPs was measured by Laser Diffraction (Mastersizer 2000, Malvern Instruments GmbH, Herrenberg, Germany) using the dry-dispersing system (Scirocco 2000, Malvern Instruments GmbH) at 4 bars. The particle sizes were analyzed according to *Mie*-theory at particle refractive index and absorption of 1.300 and 0.1, respectively. The mean values of five measurements were calculated.

Surface structures of the DEPs were determined using a scanning electron microscope (Zeiss DSM 940 A, Aalen-Oberkochen, Germany). The pictures were taken with a camera (Contax M 167 MT, Yashica-Kyocera GmbH, Hamburg, Germany) and were digitized (Orion 5, E.L.I. sprl, Brussels, Belgium). The samples were sputtered four times for 60 s and exposed to 20 mA current and 2.1 kV acceleration voltages in a vacuum of 0.02–0.03 mbar. The micrographs were taken at various magnifications using 5 and 10 kV.

The moisture sorption kinetics of the DEPs was determined using a Krüss, Processor Tensiometer K12 (Krüss GmbH, Hamburg, Germany) as well as in pyrex-desiccator humidity chambers. Various relative humidity levels (33, 44, 65, 75 and 85%) were prepared using appropriate saturated salt solutions. The moisture content of the DEPs was measured using a Karl Fischer water-titration set-up (702 SM Titrino, Deutsche Metrohm, GmbH and Co., Filderstadt, Germany). A powder bed of 1 g of the DEPs was placed in the humidity chamber and the weight gain per unit time was recorded.

The bulk and tapped densities of the DEPs were measured in a 250-mL graduated measuring cylinder. The sample contained in the measuring cylinder was tapped using a tap volumeter apparatus (model STAV 2003, J. Engelsmann AG, Ludwigshafen, Germany). The apparent particle density was determined using a Beckman air comparison pycnometer (model 930, Beckman Instruments, Munich, Germany) at room temperature. Atmospheric air was used as a comparison gas.

Angle of repose was determined by pouring 150 mL of the DEP though a funnel of 10-mm outlet diameter, adjusted at 75 mm height from the base, into 50 mm radius (r) plate placed below the tip of the funnel. The height (h) of the powder cone was measured with a dial high gauge (Mitutoyo Messgeraete GmbH, Neuss, Germany). The angle of repose (α) was calculated using the equation [$\tan \alpha = h/r$]. The mean flow rate (g/s) was determined by pouring 100 g of the DEP though a funnel of 10-mm outlet diameter with closing end. The amount of the DEP passing per unit of time under gravitational force was recorded.

The compactibility of the DEPs was determined by compressing tablets (round, flat and 10 mm in diameter) on an instrumented single punch tablet press (Korsch EK II, Korsch Pressen GmbH, Berlin, Germany). Compaction pressure was measured by a full Wheatstone bridge circuit

Table I. Composition and Characterization of the Various Tablet Formulations

Constituents	Tablet Formulations (mg)						
	I	II	III	IV	V	VI	VII
DEP (granules)	947	947	947	947	947	947	947
Avicel® PH 101	363	263	163	363	363	–	–
Avicel® PH 200	–	–	–	–	–	363	–
Cellactose® 80	–	–	–	–	–	–	363
Ac-Di-Sol®	90	90	90	–	–	90	90
Kollidon® CL	–	–	–	90	–	–	–
Explotab®	–	–	–	–	90	–	–
Properties							
Tablet weight, mg (SD)	1414.6 (9.5)	1305.6 (9.3)	1199.1 (7.1)	1420.8 (9.3)	1397.5 (10.1)	1404.1 (12.9)	1410.4 (7.6)
Crushing strength, *N* (SD)	73 (3.2)	81 (2.6)	80 (4.2)	77 (3.7)	71.3 (4.4)	72 (6.1)	78 (4.4)
Disintegration time, min (SD)	2.4 (0.7)	4.0 (0.4)	8.6 (1.1)	0.5 (0)	9.2 (1.8)	4.0 (0.5)	12.2 (1.9)

of strain gauges (type 6/120 LY 11, Hottinger Baldwin Messtechnik GmbH, Darmstadt, Germany) at the upper punch holder and by a piezo-electric load washer (type 9041, Kistler Instruments GmbH, Winterthur, Switzerland) mounted directly below the lower punch (21). Data were acquired using the MGC Plus system including a ML 10 B voltage amplifier (HBM) and the Catman software. The radial tensile strength (S) of the tablets was calculated from the thickness (H), diameter (D), and crushing strength (F_c) using the equation [$S=2F_c/\pi DH$]. The porosity (ε) of the tablets was calculated from the apparent particle density (ρ_t) and the apparent density of the tablets (ρ_a) as [$\varepsilon=1-(\rho_a/\rho_t)$]. The apparent density of the tablets was calculated from the thickness out of die, weight and diameter of the tablets (22).

Dry Granulation of the DEP by Roller Compaction

The DEP was granulated by roller compaction using Gerteis Micro-Pactor® (Gerteis AG, Jona, Switzerland). The DEP was mixed with magnesium stearate (2%) in turbula mixer (type T2C, Bachofen AG, Basel, Switzerland) at 42 rpm for 5 min. The compaction force and the roller speed were adjusted to 12 kN and 0.05 m/s, respectively. The ribbons were crushed (hand driven mill, BECO Manufacturing Co., Inc. Laguna Hills, CA) to produce granules. The particle size distribution of 50 g of granule was determined by sieve analysis on a sieve-shaker (Retak 3D, Retsch GmbH and Co KG, Haan, Germany) using 250-, 500-, 710-, and 1,000-μm sieves.

Preparation of DEP-Tablets

An instrumented eccentric tablet machine Korsch EK0 (Korsch Pressen GmbH, Berlin, Germany) fitted with oblong punches (20×8.25 mm) was used to compress the DEP-tablets. Direct compression excipients such as Avicel® PH101, Avicel® PH 200, Cellactose® 80 and disintegrants (Ac-Di-Sol®, Kollidon® CL and Explotab®) were investigated (Table I). Formulation I was further evaluated at compression forces of 13, 16, 18, 21, 24 and 28 kN.

Characterization of the DEP-Tablets

DEP-tablets were characterized for weight variation (model AE 200, Mettler Toledo GmbH, Gießen, Germany), thickness (electronic digital micrometer, Palmer, Browne and Sharpe, North Kingstown, RI), crushing strength (Erweka, model TBH-30, Heusenstamm, Germany), friability (friability tester, 25 rpm for 4 min, Type PTF 1, Pharmatest Apparatebau, Hainburg, Germany) and disintegration time (disintegration tester, six tablets in 1-L water at 37±1 °C Type PTZ 1, Pharmatest, Hainburg, Germany) according to the European Pharmacopoeia (23).

Enteric Coating of the DEP-Tablets

A batch of 1.5 kg core tablets was enteric coated in a pan coater (15-L, Erweka GmbH, Heusenstamm, Germany) with the coating suspension (Table II). Eudragit® L100–55 or Kollicoat® MAE 100P (125 g) was dissolved in *i*-propanol and acetone mixture and 1,2-propylene glycol or acetyltributyl citrate (25 g) was added as plasticizer. The insoluble ingredients (talc, titan dioxide, iron oxide and magnesium stearate) were mixed with *i*-propanol and grinded in a ball mill for 24 hours before added to the polymer solution.

The coating solution was sprayed on the core tablets (prewarmed to 25 °C) with a pressure of 1.2 bar using a two-substance nozzle (1.2 mm diameter, Düsen-Schlick GmbH, Untersiemau/Coburg, Germany). The drying temperature was set at 40 °C and the coating solution (1.5 kg) was sprayed within 90 min. After coating the tablets were dried at 30 °C for 24 h in a hot air oven (Memmert GmbH, Schwabach, Germany).

Table II. Composition of Enteric Coating Suspension

Substance	Amount (g)	Percentage (%)	Percent in Dry Film[a] (%)
Eudragit® L 100–55 *or* Kollicoat® MAE 100P	125	8.33	55.5
1,2-Propylene glycol *or* Acetyl tributyl citrate	25	1.67	11.1
i-PrOH	637.5	42.5	–
Acetone	637.5	42.5	–
Talc	42	2.8	18.7
Titan dioxide	10	0.67	4.4
Iron oxide (brown)	15	1.0	6.7
Magnesium stearate	8	0.53	3.6
Total	1,500	100	

[a] Calculated from the total dry weight of the coating suspension

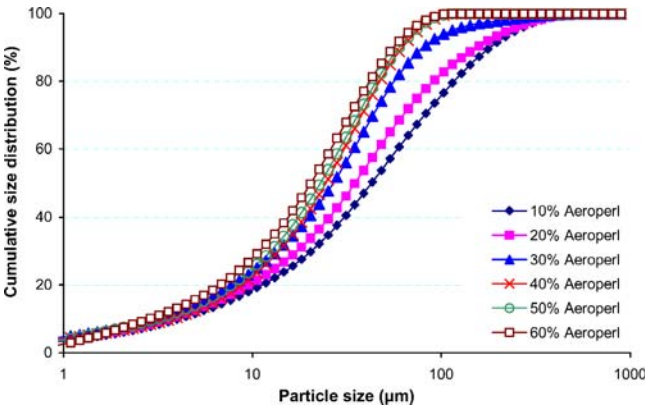

Fig. 1. Cumulative particle size distribution of the dry extract preparations of *G. lotoides* containing 10–60% Aeroperl® 300 Pharma

The disintegration time of the enteric coated tablets was determined according to the European Pharmacopoeia (23). In this, six coated tablets were first tested in 0.1 N HCl medium for 2 h and then in phosphate buffer solution pH 6.8 at 37±1°C. The stability enteric coated tablets was evaluated at 21 °C in 45% rel. humidity and 26 °C in 60% rel. humidity which approximate various climate zones. The increase in weight and thickness of the coated DEP-tablets were calculated every 24 h for 15 days.

RESULTS AND DISCUSSION

Dry Extract Preparation (DEP)

Figure 1 depicts the particle size distribution of the dry extract preparations (DEPs) containing 10–60% Aeroperl® 300 Pharma. The average particle sizes of the DEPs were found to be 46.4; 38.7; 30.1; 27.4; 25.8 and 23.1 µm for the DEPs containing 10, 20, 30, 40, 50 and 60% Aeroperl® 300 Pharma, respectively. The particle size of the dried crude extract has been reported to be 68.4 µm (14) indicating that the adsorption of the extract on Aeroperl® 300 Pharma provided smaller particles.

Scanning electron micrographs (SEM) of the DEPs revealed that the morphology of the crude extract (Fig. 2a) as well as that of Aeroperl® 300 Pharma (Fig. 2b) has been changed, due to the adsorption of the extract (Fig. 2c and 2d).

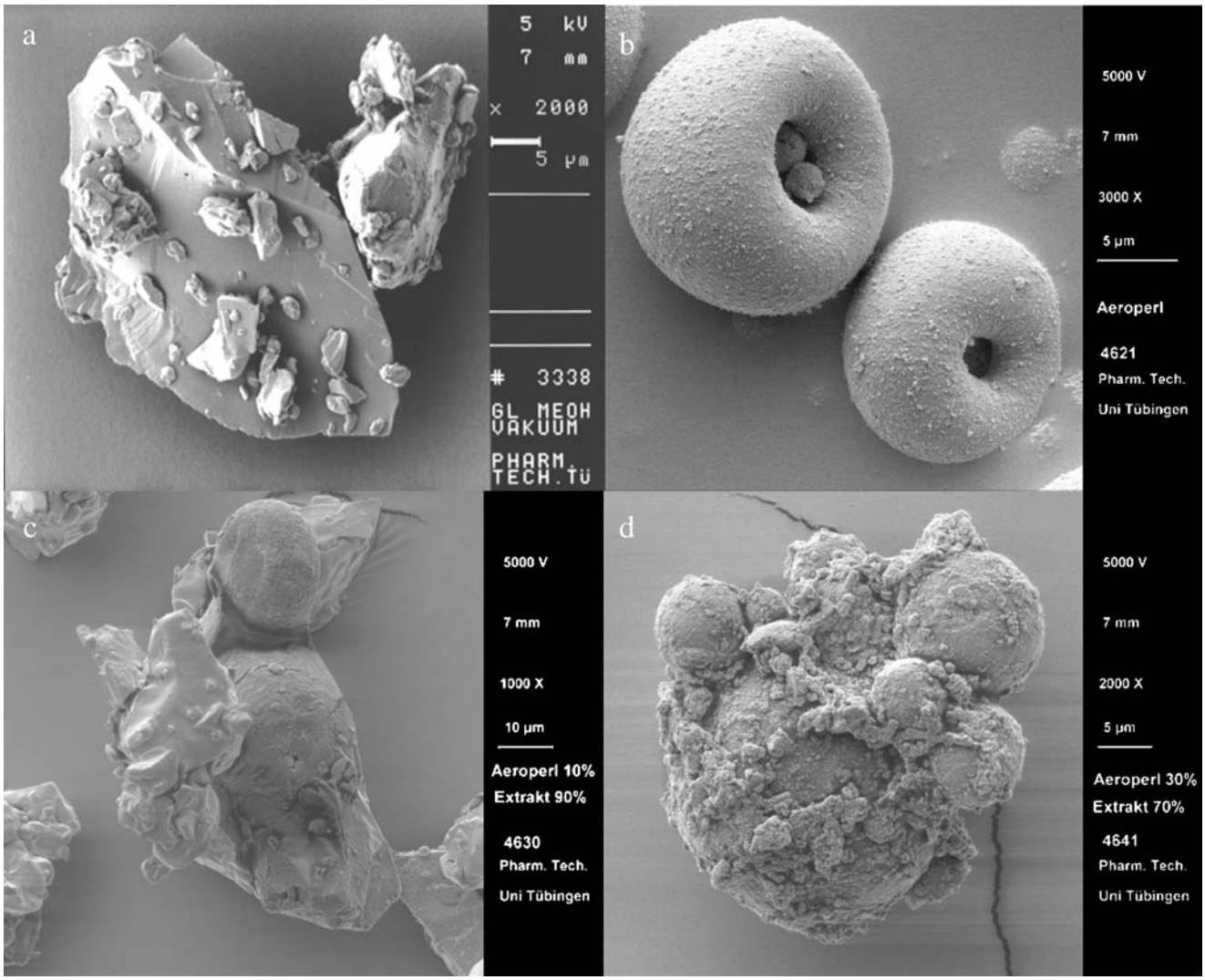

Fig. 2. Scanning electron micrographs of the **a** crude extract of the seeds of *G. lotoides* (×2,000); **b** Aeroperl® 300 Pharma (×3,000); **c** DEP containing 10% Aeroperl® 300 Pharma (×1,000) and **d** DEP containing 30% Aeroperl® 300 Pharma (×2,000)

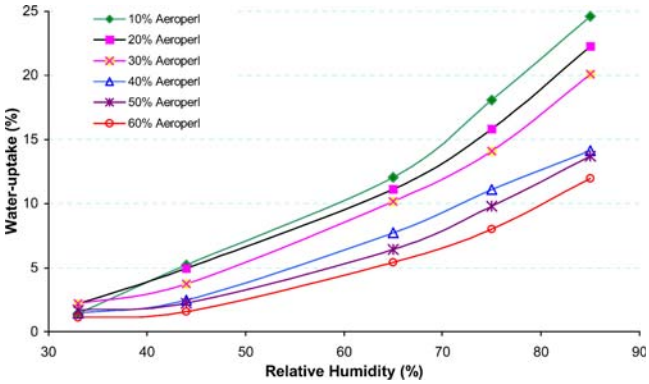

Fig. 3. Water sorption isotherm of the DEPs containing 10–60% Aeroperl® 300 Pharma (using a Krüss Tensiometer K12)

Adsorption of the crude extract had improved the irregular shape and prevented the formation of compact masses with sharp edges upon drying. The surface improvement of the extract was found to be a function of the amount of adsorbent. DEP containing 10% Aeroperl® 300 Pharma (Fig. 2c) showed surface structure similar to the crude extract (Fig. 2a), indicating that the amount of the adsorbent was not enough to alter the surface structure. Whereas, DEP containing 30% adsorbent (Fig. 2d) showed an aggregation of particles where the crude extract was adsorbed as small particles. SEM of the DEPs containing 40, 50 and 60% of adsorbent showed no significant difference.

Figure 3 depicts the water sorption pattern of the DEPs. As shown in the figure, the percentage of water adsorbed decreased with increase in the amount of adsorbent. DEPs containing 10% and 20% Aeroperl® 300 Pharma were deliquesced at relative humidity levels of 65% and above (Fig. 4). However, as shown in Fig. 4, even though DEP containing 30% Aeroperl® 300 Pharma adsorbed 20% water at 85% relative humidity the DEP remained freely flowing powder. Karl Fischer titration of the DEPs showed water content of 5.1, 4.8, 3.5, 3.3, 3.3 and 3.1% for the DEPs containing 10, 20, 30, 40, 50 and 60% adsorbent, respectively.

Based on the results of the SEM and water uptake studies, 30% Aeroperl® 300 Pharma was found to be optimal to prepare DEP for tablet formulation. Hence, the bulk characteristics of this DEP were investigated. Table III compares the densities, flow properties and compressibility

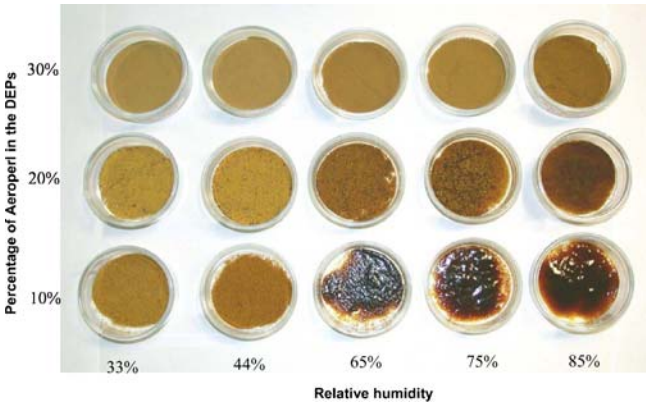

Fig. 4. Physical appearance of the DEPs containing 10, 20 and 30% Aeroperl® 300 Pharma after 15 days in 33, 44, 65, 75 and 85% relative humidity chambers

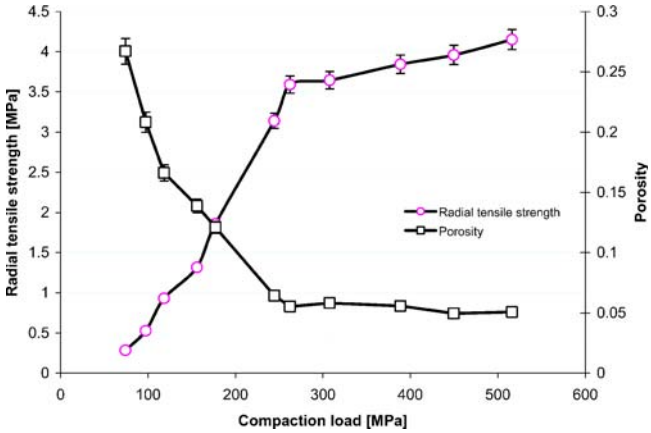

Fig. 5. Radial tensile strength and porosity of the dry extract preparation at various compression pressures

index of the crude extract and the DEP. As shown in the table, due to the adsorption of the extract on Aeroperl® 300 Pharma, the bulk density increased while the tapped density decreased indicating the improvement in flow properties. Porosity and Carr's compressibility index (%)=[(tapped density-bulk density)/bulk density]×100 which are measures of compressibility and flow properties were calculated. Due to the conversion of the crude extract into DEP, the consolidation index had decreased form 29.8 to 19.9, indicating the improvement of the flow property. Compressibility indices less than 15% are indicative of free-flowing powders and indices greater than 40% usually correspond to very poor flow (24).

Dry plant extracts usually show poor flowability. The poor flow property of the crude extract of the seeds of *G. lotoides* has been reported earlier (14). As shown in Table III, the DEP showed an angle of repose 36.2° which is classified as passable (fair) flow (24) and the flow rate was found to be 7.9 g/s. The crude extract did not flow through a funnel of 10-mm aperture under gravitational force and showed an angle of repose of 43.7°. Scanning electron micrograph of the DEP (Fig. 2d) showed that the rough and irregular particle shape of the crude extract (Fig. 2a) have been converted into aggregated spherical DEP particles that promote free flow (25).

The relationships between the compression pressure, radial tensile strength and porosity of the DEP-tablets are

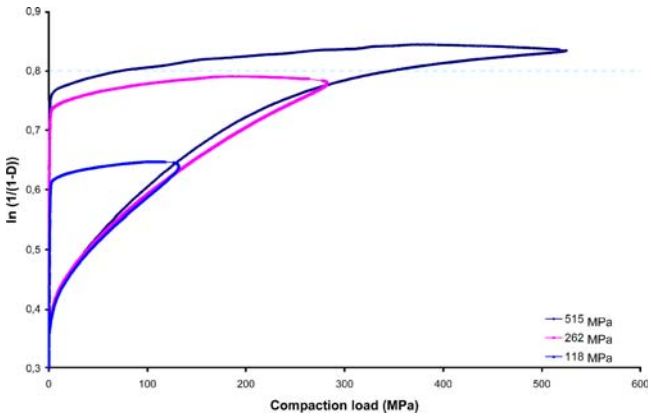

Fig. 6. Heckel plots of the dry extract preparation at compression pressure of 118, 262 and 515 MPa

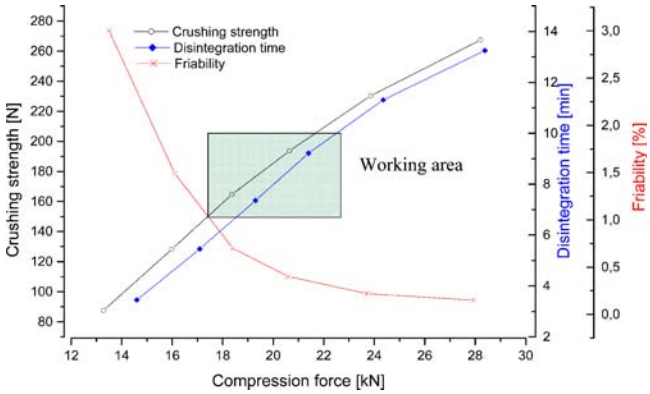

Fig. 7. Effect of the compression force on the crushing strength, disintegration time and friability of DEP tablets

depicted in Fig. 5. As shown in the figure, the tensile strength of the tablets increased while the porosity decreased, with increase in compression pressure up to 260 MPa. The change in these tablet properties was minimal beyond the compression pressure of 260 MPa. Moreover, the tablets showed no sign of capping and lamination even at higher compression pressures indicating the high plastic deformation of the DEP. The Heckel plots of the DEP at compression pressures of 118, 262 and 515 MPa are shown in Fig. 6. The mean yield pressures (reciprocal of the slope of the linear region), which show the minimum pressure required to cause deformation, were found to be 661, 808 and 874 at compaction pressure of 118, 262 and 515 MPa, respectively. The initial curved region of the Heckel plots can be explained on the basis of particle rearrangement, which results from a decrease in void volume. There can be some fragmentation during this initial stage. Beyond the particle rearrangement phase, powder densification occurs linearly as a function of applied pressure. The particle deformation is completely reversible if the applied pressure is below the elastic limit of the material. However, at higher pressures, permanent deformation occurs either through plastic flow or fragmentation (26).

Dry Granulation by Roller Compaction

Processing of powders into granules or aggregates is commonly performed in order to modify the flowability and compactibility as well as the disintegration time (27). One of the processes of densification of powders is granulation by roller compaction (28).

The tablets prepared form the crude extract of the seeds of *G. lotoides* showed a prolonged disintegration time (14). Moreover, large amounts of the extract were required to achieve the traditional dose. These conditions necessitate the need for granulation of the DEP by compaction. Rocksloh *et al.* have reported that granulation by roller compaction of plant extracts before compression had improved both the disintegration time as well as crushing strength of the tablets (29).

Granulation of the DEP provided granules with particle sizes between 250 and 710 μm. Sieve analysis of the granules depicted that the amount of fines (less than 250 μm) and particles greater than 1.00 mm were found to be 6.3 and 1.4%, respectively. The flowability of DEP was further improved by the granulation process (Table III). As shown in the table, the granules of the DEP exhibited relatively high bulk and tapped densities, and the compressibility index was found to be 7.3%, which is considered as an excellent flow property (24).

Formulation of DEP Tablets

DEP tablets containing 947 mg of granules were compressed according to the formulations shown in Table I. Avicel® PH 101, Avicel® PH 200 or Cellactose® 80 was used as filler/binder and Kollidon® CL, Explotab® or Ac-Di-Sol® was used as disintegrant. The 2% magnesium stearate which is included into the DEP before granulation by compaction was sufficient to prevent sticking of the tablet mixture to the punch faces. The crushing strength of the tablets was maintained in the range of 70 to 80 N.

The effects of the type and amounts of filler/binder and disintegrant were evaluated considering disintegration time as a response. As shown in Table I, Avicel® PH 101 provided tablets with disintegration time of 2.4 min, whereas tablets prepared with Avicel® PH 200 and Cellactose® 80 showed disintegration times of 4.0 and 12.2 min, respectively. Tablet Formulations I, II, and III (Table I) compare the effect the amount of Avicel® PH 101. The disintegration time of the tablets decreased from 8.6 to 2.4 min with increase in the amount of Avicel® PH101 from 163 mg (I) to 363 mg (II) for tablets prepared with comparable compression force. ANOVA shows that the disintegration time of the formulations were significantly different ($p=0.05$) with a higher F-value of 96.5.

The influence of various disintegrants namely Kollidon® CL, Explotab® and Ac-Di-Sol® was evaluated (I, IV and V).

Table III. Compressibility and Flow Properties of the Crude Extract of the Seeds of *G. lotoides*, DEP and its Granulation by Roller Compaction

Properties	Crude Extract of *G. lotoides*	Dry Extract Preparation (DEP)	
		Powder	Granule
Densities, g/mL (SD)			
Bulk	0.663 (0.0015)	0.697 (0.0012)	0.742 (0.0010)
Tapped	0.942 (0.0030)	0.870 (0.0047)	0.796 (0.0069)
Apparent	1.513 (0.0023)	1.547 (0.0021)	–
Angle of repose, ° (SD)	43.7 (2.85)	36.2 (2.16)	31.2 (1.72)
Flow rate, g/s (SD)	Does not flow	7.94 (1.69)	10.33 (1.77)
Porosity (%)	56	55	–
Carr's index (%)	29.8	19.9	7.3

As shown in Table I, tablets prepared with Kollidon® CL disintegrated within 30 s, while tablets containing Explotab® and Ac-Di-Sol® showed disintegration times of 9.2 and 2.4 min, respectively. However, tablets prepared with Kollidon® CL adsorb moisture and disintegrate when they are stored at room temperature in an open container.

Based on the results discussed earlier, tablet formulation containing DEP (947 mg), Avicel® PH101 (363 mg) and Ac-Di-sol (90 mg) was further evaluated. Figure 7 depicts the effect of compression force on the crushing strength, disintegration time and friability of the DEP tablets. Due to the complex geometry of the oblong tablets, compression pressure, porosity and tensile strength of the tablets were not calculated. As shown in figure, the crushing strength of the tablets increased with increasing compression force without any sign of capping or lamination at higher compression forces. On the other hand, friability decreased rapidly as the compression force increased. The target friability of less than 1% was obtained at compression forces of above 18 kN. A disintegration time of less than 10 min was set as a target which together with the friability defines the working area (shaded part in Fig. 7).

Enteric Coating of DEP Tablets

Enteric coating of DEP tablets would provide an immediate release of the active components of the plant in the small intestine, where it acts as anthelmintics as well as protects the tablets from atmospheric humidity due to the hygroscopic nature of the extract.

DEP core-tablets were prepared at a compression force of 20 kN as described earlier. The core-tablets showed a crushing strength of 195 N, a disintegration time of 9 min and a friability of 0.4%. The formulation of the enteric coating suspension is given in Table II. EUDRAGIT® L 100-55 or Kollicoat® MAE 100P which dissolve from pH 5.5 upwards was used as enteric coating polymer. 1,2-Propylene glycol and acetyl tributyl citrate were investigated for the plasticizer activity. Based on the ease of coating and properties of the coated tablets, 1,2-propyene glycol (11% in dry film) was selected as plasticizer. Similar findings were reported by Flößer *et al.* (30) who have evaluated the effect of plasticizer types and quantity on the preparation, processing and properties of isolated films and film-coated caffeine tablets. They found that of all the plasticizers investigated (i.e., propylene glycol, polyethylene glycol 400, 6,000, 1,500, and triethyl citrate), the formulation with 20% propylene glycol performed the best (30).

The gastro-resistance test was performed in a tablet disintegration tester according to the EP (23). The enteric coated tablets resisted disintegration or softening in simulated gastric fluid (0.1 N HCl) for a minimum of 2 h. The tablets were then inspected for signs of disintegration and cracks that might lead to premature release of the active ingredients. Subsequently, the test fluid is replaced with phosphate buffer solution pH 6.8 and the coated tablets disintegrated within 15 min. Significant difference was not observed in disintegration time of tablets coated with Eudragit® L 100/55 or Kollicoat® MAE 100P.

The physical stabilities of the enteric coated DEP-tablets were evaluated at different storage conditions. At 26°C and 60% RH, the enteric coated tablets showed a 6% *w*/*w* tablet weight increase and thereby 8% increase in tablet thickness after 15 days. Whereas, the uncoated core-tablets absorbed up to 10% *w*/*w* water and showed 13% increase in tablet thickness. At 21°C and 45% RH, the water uptake was less than 2% for the enteric coated tablets and 4% for the cores. The adsorption equilibrium was reached within 5 and 15 days for the core and enteric coated tablets, respectively.

CONCLUSION

The results of this investigation showed that adsorption of the liquid extract of the seeds of *G. lotoides* on Aeroperl® 300 Pharma (30% *w*/*w*) resulted in free-flowing non-adherent powder. Granulation by roller compaction of this powder has further improved the flow properties and the disintegration time of the tablets thereof. Oblong tablets which could administer the traditional dose as a single tablet have been developed and enteric coated using methacrylic acid/ ethyl-acrylate co-polymers.

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