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Research Article

A Systematic Study on Processing Problems and *In-vitro* Release of *Saraca indica* Caesalpiniaceae Bark Powder Tablets

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Abstract

Purpose: *To examine the original flowability, compressibility and compactibility of Saraca indica bark powder and its tablet formulations.*
Methods: *Saraca indica bark powder was subjected to various quantitative tests including acid insoluble ash, total ash, foreign organic matter, alcohol soluble extractive and water soluble extractive. Its flowability and compressibility were determined using Kawakita, Heckel and Leuenberger relationships. Tablets were prepared from the powder by direct compression and wet granulation techniques and characterized.*
Results: *Kawakita analysis revealed lower cohesiveness of granules (3.877 ± 0.890) compared to the powder (6.176 ± 1.030), and hence improved flowability. From Heckel analysis, the higher value of intercept (A) for granules (4.38 ± 0.45) implies higher degree of fragmentation than direct compression DC formulation (2.90 ± 0.33) and powders (2.44 ± 0.12). The compression susceptibility parameter obtained from Leuenberger equation for compacts formed by wet granulation technique (0.183 ± 0.045 1/kg/cm^2) indicate that maximum crushing strength is reached faster at lower pressures of compression than for Saraca indica bark powder (0.073 ± 0.025 1/kg/cm^2) and DC formulation (0.105 ± 0.033 1/kg/cm^2). In-vitro dissolution study showed that more than a 90% of tannin was released within 30 and 60 min from tablets prepared by wet granulation and DC, respectively. Brittle fracture index data indicate that tablets prepared from granules showed less fracture, capping and lamination tendencies.*
Conclusion: *It is concluded that the desired flowability, compressibility and compactibility of Saraca indica bark powder can be obtained by direct compression and wet granulation techniques.*

Keywords: *Saraca indica, Flowability, Powder, Tablets, Compressibility, Dissolution.*

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INTRODUCTION

The dried stem bark powder of *Saraca indica* (family: Caesalpiniaceae) is a claimed wonder herb that cures several diseases. It is extensively used in India's Ayurvedic system of medicine for the treatment of a variety of ailments such as excessive uterine bleeding and stomachache, and as a blood purifier, hypothermic and diuretic. *Saraca indica* is an excellent herb for the therapy of gynecological problems including uterine bleeding associated with fibroids, leucorrhoea and menstrual disturbances without producing any side effects. It is also used for stimulating uterus, endometrium and ovarian tissues. Other ailments it is used to treat are internal piles, diabetes, dyspepsia, indigestion, burning sensation, blood disorders, fractures, tumors, bites, ulcerations, and skin discoloration [1,2].

In spite of their efficacy, herbal medicinal products have been widely criticized due to lack of standardization and poor-quality presentation. Formulation of *Saraca indica* into a modern pharmaceutical conventional tablet dosage form would confer on it many of the properties of a good tablet, including ease of administration, greater patient acceptance, prolonged shelf life, quality assurance, greater accuracy in dispensing and reduction in transportation cost arising perhaps from powder formulation into less bulky tablet dosage form [3].

The measurement of porosity changes as a function of compression pressure is widely used in describing powder compressional behavior. The compressibility of a powder bed could be inferred from the relationship between porosity and applied pressure [4]. Due to poor flowability and compressibility, *Saraca indica* bark powders necessarily require alteration prior to tableting. These parameters become more critical when the formulation contains a large amount of active substance with poor compressional properties. However, there are no reports in the literature on the optimization of micromeritic properties of *Saraca indica* for processing into tablet dosage form. Therefore, the aim of present study was to develop suitable conventional tablets of *Saraca indica* bark powder for oral administration using wet granulation and direct compression methods, as well as to assess its flow and compression characteristics [5].

EXPERIMENTAL

Materials

Standard tannin was obtained *gratis* from Sami Labs, India. Avicel PH 101 and 102 (FMC Corporation, Philadelphia, USA), cross-caramelose sodium and dicalcium phosphate were also obtained *gratis* from Mitushi Pharma Gujarat, India. All other chemicals used were of analytical grade.

Collection of plant material

The barks of *Saraca indica* were collected from the campus of College of Pharmaceutical Sciences, Mohuda, India and was authenticated by Prof SK Dash, PG Dept of Biosciences, Berhampur University, India. A voucher specimen (0623/10/PGDB/BU) was deposited in the department's herbarium for future reference. The barks were dried under shade, powdered and passed through nominal mesh with aperture of 180µm.

Phytochemical characterization of the plant powder

The *Saraca indica* bark powder was subjected to various phytochemical analysis including acid insoluble ash, total ash, foreign organic matter, alcohol soluble extractive and water soluble extractive [6]. Mean tannin was determined using a UV-Visible spectrophotometer (UV-2450, Shimadzu, Japan) at λ_{max} 274 nm [7].

Preparation of granules

The wet granulation method of massing and screening was used with a batch size of 1000

tablets. *Saraca indica* bark powder (500 g), Avicel pH101 (50 g) and starch (25 g) were dry mixed in a wet granulator (WGS, Kalweka Series, Karnavati Engineering Ltd, India). The dry mix was moistened with an appropriate amount of cross-caramelose slurry (5 %), mixed well in the granulator and passed through a sieve with aperture of 1000µm. The granules were dried in a hot air oven (Hicon India Ltd, India) for 4 h at 60 ^{0}C and then re-sieved through sieve with aperture of 1000µm. Talc and magnesium stearate (1 %w/w) were added and mixed for 4 min in a cube mixer (Kalweka series, Karnavati Engineering Ltd, India).

Preparation of direct compression (DC) formulation

In direct compression method, *Saraca indica bark* powder (500 g), Avicel pH 102 (75 g), dicalcium phosphate (25 g) and talc (10 gm) were mixed in a cube mixer (Kalweka series, Karnavati Engineering Ltd, India) based on a batch size of 1000 tablets.

Fundamental powder and granule properties

Bulk and tap density

The bulk and tap density of *Saraca indica bark* powder and formulations was determined by tapping method (n = 10) using data obtained from a digital tap density apparatus (Electrolab Ltd, India).

Flow rate

The flow rate [8] of the *Saraca indica bark* powder and the granules were determined as the ratio of mass (g) to time (seconds) using a steel funnel with an orifice diameter of 10 mm (n = 10).

Kawakita analysis

Flowability was determined using the Kawakita analysis [9]. The bark powder or formulation (10 g) was poured into a 50 ml glass measuring cylinder, the heap of the particles in the cylinder was leveled off horizontally with a thin metallic spatula, and the bulk volume, *Vo*, was accurately measured. The cylinder was then tapped mechanically and the change in volume of the powder column, $V_{N,}$ was noted after tapping. The compactibility and cohesiveness of both the powder and granules were evaluated using numerical constants obtained from the Kawakita plots based the Kawakita equation, which is used for assessing the flow properties of powders (Eq 2).

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \quad \text{..... (2)}$$

where *a* and *b* are constants; *a* describes the degree of volume reduction at the limit of tapping and is called compactibility; *1/b* is considered to be a constant related to cohesion and is called cohesiveness, *C*. The degree of volume reduction was calculated from the initial volume (V_0) and tapped volume (V_N) as in Eq 3.

$$C = \frac{(V_0 - V_N)}{V_0} \quad \text{..... (3)}$$

Numerical values for constants *a* and *1/b* were obtained from the slope of plots of *N/C* versus number of taps *N (N* = 10, 20, 30, up to 300*)*.

Preparation of compacts

Compacts containing 500 mg of *Saraca indica* were made from either the bark powder, wet granulated or direct compression formulations, using a hydraulic pellet press (Kimaya Engineers, India) at compression loads ranging from 10 to 95 kg/cm^2. Ten flat-faced 13 mm diameter compacts were made at each compression load. Prior to compression, the die and punches were lubricated with a 2 %w/v dispersion of magnesium stearate in ethanol/ether (1:1). The compacts were stored over silica gel for 24 hours (to allow for elastic recovery and hardening, and thus avoid false low yield values) prior to evaluation. The dimensions (thickness and diameter) and weight uniformity of three compacts were

determined. The relative density (ρ_r) was calculated as the ratio of apparent density (ρ_A) of the compact to the true density (ρ_T) of the powder as in Eq 4

$$\rho_r = \frac{\rho_A}{\rho_T} \quad \text{..... (4)}$$

Heckel analysis

The data obtained were applied to obtain Heckel plots. Linear regression analysis was carried out over a compression range of 10 to 95 kg/cm^2 and parameters from Heckel plots [10] were calculated. The compaction characteristics of the powder were analysed with Heckel equation (Eq 5).

$$\ln \frac{1}{1-\rho_r} = KP + A \quad \text{..... (5)}$$

where, ρ_r is the relative density of the compact, *P* the applied pressure, *K* (the slope of the linear portion of the plot) the reciprocal of the yield pressure, *Py*, of the material, and A (intercept). The yield pressure is inversely related to the ability of the material to deform plastically under pressure and *A* is a function of the original compact volume.

Leuenberger analysis

For compactibility assessment, the force required for diametral breaking of the compacts was determined using a digital hardness tester (EH-01, Electrolab Ltd, India). Tensile strength (σ_x) of the compacts was calculated using Eq 6 [11].

$$\sigma_x = \frac{2x}{\pi dt} \quad \text{(6)}$$

where, x is hardness (in kg/cm^2), and *d* and *t* are the diameter and thickness of the compacts (in mm), respectively. Leuenberger analysis was performed by fitting the data to Eq 7 [12]. A nonlinear plot of tensile strength versus the product of compaction pressure (*P*) and relative density (ρ_r) was obtained using a software (Graph Pad Prism 4).

$$\sigma_x = \sigma_{x\max}(1 - e^{-\rho_r \times \gamma \times P}) \quad \text{..... (7)}$$

where $\sigma_{x\max}$ is maximum tensile strength (kg/cm^2) when *P* will be infinite and ρ_r will be equal to 1, and γ is compression susceptibility.

Preparation of tablet

Tablets containing 500 mg of *Saraca indica bark* powder were produced by compressing the granules using a single station tablet punching machine (Cadmach Machinery Co Pvt Ltd, India) equipped with 13 mm circular, flat–faced punches.

Determination of brittle fracture index (BFI)

Crack theory can be used to develop a quantitative expression for the measurement of the brittle fracture tendency [13]. The BFI values of the tablets were obtained from Eq 8 [14].

$$BFI = 0.5\left(\frac{T}{T_0} - 1\right) \quad \text{.....(8)}$$

where To and T are the tensile strengths of tablets with and without a central hole, respectively. The centre hole (≤ 1.2 mm) is a built-in model defect to simulate actual void formed in the tablet during compression. For brittle fracture to occur, the ratio T/To = 3. By subtracting 1 and multiplying by 0.5, the maximal BFI value is 1 (unity). The BFI value thus has a range of 0 (no fracture tendency) to 1 (maximal fracture tendency). Tablet samples with BFI values (≥ 0.5) display a high fracture incidence during actual tableting.

Physical characterization of tablets

Saraca indica bark powder tablets prepared by wet granulation and direct compression were subjected to some physical tests. Weight variation was determined by weighing 20 tablets individually, the mean weight was

calculated and the percent variation of each tablet from the mean was determined. Hardness was determined with a digital tablet hardness tester (Electrolab Pvt Ltd, India) on 6 randomly selected tablets from each formulation and the mean applied pressure (kg/cm^2) to crush the tablets was computed. Friability was determined by first weighing 10 tablets and placing them in a friability tester (Electrolab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dusting the tablets, their total weight was again recorded and the percent weight difference recorded as friability. The disintegration time of six tablets per formulation was determined in 900 ml of distilled water using a disintegration test apparatus (Electrolab Pvt Ltd, India).

In-vitro dissolution test

Release of pure tannin [15] from the tablets of *Saraca indica bark* powder was determined using a USP XXI six-station dissolution test apparatus I (Disso 2000, Labindia) at 50 rpm. The dissolution medium was 900 ml 0.1M HCl and the temperature was maintained at 37 ± 0.2 ^{0}C. Samples of 5 ml each were withdrawn at 5, 10, 20, 30, 40, 50 and 60 min time intervals, filtered through Whatman filter (0.45 µm, Auroco Pvt Ltd, Thailand) and replaced with an equal amount of fresh dissolution medium in each instance. The samples were suitably diluted and analyzed for tannin content using a UV/Visible double-beam spectrophotometer (UV-2450, Shimadzu, Japan) at 274 nm. The amount of tannin was calculated from the calibration curve of standard tannin. The release studies were conducted in triplicate**.**

Statistical analysis

Statistical analysis was carried out on the data to determine the differences between the bark powder and its formulations prepared by wet granulation and direct compression. This was achieved by carrying out a one-way ANOVA at $p < 0.05$ level using software GraphPad Prism® 4 software (GraphPad Software Inc, San Diego, USA). At a 95 % confidence interval, a calculated f-value of more than the critical f-value was considered significant. Paired t-test was carried out to ascertain any significant difference between release data for formulations prepared by wet granulation and direct compression. At a 95 % confidence interval, t-values less than or equal to the critical t-value were considered significant.

RESULTS

Basic powder parameters and drug content

Acid insoluble ash (0.70 ± 0.25 %), total ash (5.5 ± 1.0 %), alcohol soluble extractive (40.0 ± 1.5 %) and water soluble extractive (65.9 ± 2.5 %) were within the limits of Ayurvedic Pharmacopoeia of India [6]. Mean content of tannin in 100 mg of bark powder was 30 ± 2 mg calculated as tannin with reference to the tannin reference standard [7].

Physicochemical properties of powder and granule

The flow rate of direct compression formulation (1.46 ± 0.57 g/sec) and granules (2.58 ± 0.11 g/sec) indicate that there was a significant difference ($p < 0.05$) in flowability between the two forms. Thus, the flow properties of *Saraca indica* bark powder were poor for direct processing into tablet dosage form. Bulk density and tapped density were 0.253 ± 0.010 and 0.385 ± 0.050, 0.285 ± 0.051 and 0.415 ± 0.025, 0.361 ± 0.040 and 0.456 ± 0.090 g/cm^3 for powder, direct compression formulation and granules, respectively.

Kawakita data

Plots of *N/C* versus *N* (Kawakita plots) for *Saraca indica* bark powder, direct compression formulation and granule gave a linear relationship in each case. The constants, *a* and *1/b*, of the Kawakita equation were resolved from the slope and intercept of the line plot of *N/C* versus *N*,

Table 1: Heckel data for the preparations

Preparation	Slope (K)	Intercept (*A*)	Yield pressure (*Py*)	Coefficient of determination (r^2)
Bark powder	0.078 ± 0.004	2.439 ± 0.120	220 ± 5	0.9956
DC formulation	0.081 ± 0.003	2.898 ± 0.330	180 ± 5	0.9984
Granules	0.099 ± 0.006	4.380 ± 0.450	150 ± 4	0.9932
f-value	333*	1637021*	6666*	
F-critical	5.1432	5.1432	5.1432	

Note: *All values are expressed as mean ± SD, n = 10; * Significant difference at p < 0.05 level*

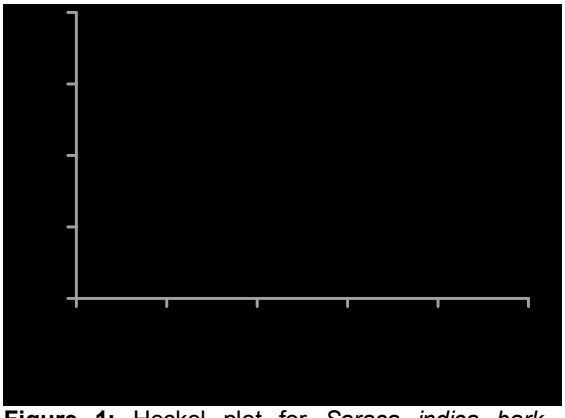

Figure 1: Heckel plot for *Saraca indica bark* powder (◊), direct compression formulation (▼) and granules (Δ); mean ± SD, n = 10).

and found to be 0.376 ± 0.087 and 6.176 ± 1.030 for powders, 0.304 ± 0.088 and 5.443 ± 1.230 for DC formulations and 0.209 ± 0.046 and 3.877 ± 0.890 for granules, respectively.

Heckel data

Heckel data (Figure 1 and Table 1) for direct compression formulation and granule show no linearity at the early stages of compression due to particle rearrangement and the initial fragmentation. The higher value of intercept (*A)* for granules (4.38 ± 0.45) implies a higher degree of fragmentation than for DC formulation (2.90 ± 0.33) and powder (2.90 ± 0.33). When the compression pressure was increased, the granules showed plastic deformation [16]. The greater slope indicates a greater degree of plasticity of granules (0.099 ± 0.006) than those of DC formulation (0.081 ± 0.003) and powder (0.078 ± 0.004), hence better compressibility of the granules.

Leuenberger analysis

The compression susceptibility data (Figure 2c) for compact formed by wet granulation technique (0.1825 ± 0.045 1/kg/cm^2) indicate that the maximum crushing strength was reached faster at lower pressures of compression compared to bark powder compact (0.073 ± 0.025 1/kg/cm^2), as shown in Figure. 2a. Table 2 demonstrate that granules produced higher tensile strength (7.40 ± 0.36 kg/cm^2) than direct compression formulation (3.48 ± 0.63 kg/cm^2) and powder (0.98 ± 0.45 kg/cm^2), and this shows that granules of the plant bark was capable of yielding a compact with a higher strength than direct compression formulation (Figure. 2b).

The one-way ANOVA data in Tables 1 and 2 show that the calculated f-value was much higher than the critical f-value for all the parameters (p < 0.05), thus indicating that there was significant improvement in flowability and compressibility following granulation.

Physical characteristics of the tablets

All the batches of tablets were produced under similar conditions to avoid processing variables. Weight variation for the *Saraca indica* tablets prepared by wet granulation and direct compression method were in the range of 600 ± 14 and 610 ± 16 mg, respectively, while tablet hardness was higher for tablets prepared by wet granulation

Table 2: Leuenberger data for the preparations

Preparation	Compression susceptibility, γ (1/kg/cm^2)	Maximum tensile strength , $\sigma_{x\max}$ (kg/cm^2)	Coefficient of determination (r^2)
Bark powder	0.07324 ± 0.025	0.9773 ± 0.45	0.9429
DC formulation	0.105 ± 0.033	3.48 ± 0.63	0.8542
Granules	0.183 ± 0.045	7.40 ± 0.36	0.6262
f-value	100775*	70130574*	
F-critical	5.1432	5.1432	

Note: *All values are expressed as mean ± SD, n=10; *Significant difference at p < 0.05*

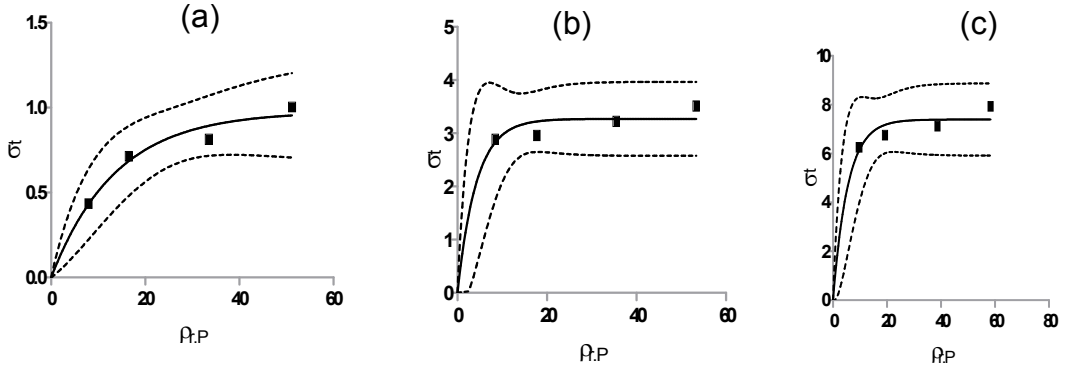

Figure 2: Plot of radial crushing strength against the product of pressure of compression pressure and relative density of *Saraca indica* bark for (a) powder (b) direct compression formulation, and (c) granules

(5.50 ± 1.15 kg/cm^2) than by direct compression (4.60 ± 1.31 kg/cm^2), and tablet thickness was 3.90 ± 0.05 and 4.10 ± 0.06 mm, respectively. Other data for tablets prepared by direct compression and wet granulation were 0.77 ± 0.28 and 0.43 ± 0.16 %, respectively, for friability; and 12.0 ± 1.5 and 15.0 ± 1.9 min, respectively, for disintegration time.

Brittle fracture index

The brittle fracture index (BFI) was 0.294 and 0.398 for tablets prepared by wet granulation and direct compression methods, respectively.

In-vitro dissolution

As Figure 3 indicates, more than 90 % of tannin was released within 30 min from tablets prepared by wet granulation while DC tablets released more than 90 % of tannin within 60 min.

DISCUSSION

Fundamental powder and granule properties

One of the most important factors affecting bulk density of a powder and its flow properties is interparticulate interaction (8). Suboptimal presence of water diminishes the cohesiveness of powder, resulting in increased bulk density for granule and direct compression formulations and hence, enhanced flowability (17). On the other hand, increased tapped density of granule and direct compression formulation indicate better degree of compactibility as a function of applied pressure (18).

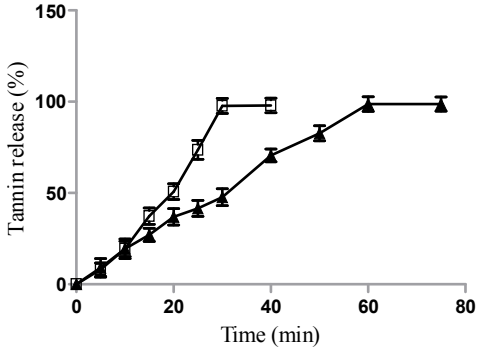

Figure 3: Dissolution profile of tablets of *Saraca indica* bark prepared by wet granulation (□) and direct compression (▲) in simulated gastric fluid (SGF).

From Kawakita analysis, it was found that granules densified the least (small compressible value) but attained the final packing state more slowly than DC formulation and powder. The lower values of *a* and 1/b for the granule formulation indicate better flowability and lesser cohesiveness than the direct compression formulation (19).

Heckel analysis showed that granule formulation exhibited higher value for die filling in the initial stages of rearrangement, as indicated by *A* (intercept) value. This behaviour could result in the formation of bridges and arches, which would in turn prevent close packing of the particles in the bulk state. Hence, mean yield pressure, *Py*, values were lower for the granule formulation than for the other formulations (Table 1). The results, therefore, indicate that the granules underwent plastic deformation more easily than the direct compression (DC) formulation. This also confirms that the direct compression formulation is somewhat resistant to deformation.

Leuenberger analysis allow maximum tensile strength and compression susceptibility to be applied to facilitate the characterization of the different materials (20). The low maximum tensile strength of *Saraca indica* bark powder indicate poor bonding properties. In this regard, *Saraca indica* granule and DC formulations showed moderate bonding properties. More than 90 % of the drug was released within 30 min for tablets prepared by wet granulation method compared with 60 min for DC formulations.

BFI data revealed that tablets prepared from granules exhibited lower fracture, capping and lamination tendencies [14].

CONCLUSION

Both wet granulation and direct compression methods can be used successfully for developing suitable tablet formulations of *Saraca indica* bark. The approach employed in this study may be applicable to the development of other herbal drugs and ayurvedic formulations, into suitable tablets.

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