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Brief/Technical Note

Applicability and Comparative Evaluation of Wet Granulation and Direct Compression Technology to *Rauwolfia serpentina* Root Powder: A Technical Note

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KEY WORDS: compressibility; flowability; *Rauwolfia serpentina*; tablets.

INTRODUCTION

The dried root of *Rauwolfia serpentina*, family Apocynaceae is well accepted that the pharmacological effects are due to its alkaloids, especially the reserpine-rescinnamine group (1,2). It is principally used in treatment of mild hypertension (3), tranquilizer for nervous and mental disorders (4,5). Preliminary investigations of its pharmacological activities justify its use in folk medicine. The dose of *R. serpentina* powder is 200 mg daily in divided doses for 1–3 weeks (4). Dispensing and consumption of powder formulation is inconvenient to the patients. Hence there is an urgent need for the development of systematic study on methods for standardization of traditional medicine has led to the formulation of *R. serpentina* powder into tablet dosage form.

The measurement of porosity change as a function of compression pressure is widely used in describing the powder compressional behavior. The compressibility of a powder bed could be inferred from the relationship between porosity and applied pressure (6). Due to poor flowability and compaction behavior, *R. serpentina* powder frequently requires alteration prior to tabletting. Direct compression of powders requires materials exhibiting good flowability, comapactibility and compressibility. These parameters become more critical when the formulation contains large amount of active substances with poor compressional properties. Wet granulation method is selected for production of porous and free-flowing granules, which enables to form tablets with high mechanical strength at low compression pressure.

In the present study, attempts were made to develop tablet formulations of *R. serpentina* powder through alteration of particle size by granulation and direct compression technique after a systematic study on flowability, compactibility and compressibility (7) with an aim to characterize the consolidation behavior.

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MATERIALS

The root of *Rauwolfia serpentina* was collected from vicinity regions of Mohuda, India and was identified and authenticated by Botanist of PG Dept of Biosciences, Affiliated to Berhampur University, India. The voucher specimen (0123/07/PGDB/BU) has been deposited in their repository herbarium. The root was dried under shade and finally powdered and sieved through sieve no. 85/100. USP reserpine reference standard was purchased from Phytolipids Pvt. ltd. India. Avicel PH101 and Avicel PH 102 were the gratis samples received from Ranbaxy Lab ltd. India. Starch RX 1500 was obtained as gratis sample from Colorcon, India. All other chemicals used were of analytical grade.

METHODS

Determination of Quantitative Standards and Drug Content

The *R. serpentina* root powder was subjected to various quantitative tests such as loss on drying, acid insoluble ash and foreign organic matter, compared with the official standards (8). Average combined content of reserpine and rescinnamine was determined by liquid chromatography with multiwavelength fluorescence detector (9) (model 2475, Waters).

Preparation of Granules

The wet granulation method of massing and screening was used with a batch size of 100 tablets. *R. serpentina* root powder (70% *w*/*w*) and Avicel pH101 (25% *w*/*w*) were dry mixed for 5 min in a Wet Granulator WGS (kalweka Series, Karnavati Engineering Ltd, India). The dry mix was moistened with an appropriate amount of 5% starch paste (*w*/*v*) and subjected to wet mixing for 7 min in the same wet granulator. The wet mass was passed through sieve no. 16. The granules were dried in a Hot Air Oven (Hicon India Ltd, India) for 4 h at 60° C and then re-sieved through sieve no.16. Talc and magnesium stearate was added and mixed for 4 min in a Cube mixer (Kalweka series, Karnavati Engineering Ltd, India).

Preparation of Direct Compression Formulation

In direct compression method *R. serpentina* root powder (80% *w/w*), Avicel pH102 (11% *w/w*), starch RX1500 (7%) and talc (2%) were mixed for 10 min in a Cube mixer (Kalweka series, Karnavati Engineering Ltd, India).

Fundamental Powder Properties

True Density

The true densities of the *R. serpentina* powder and formulations were determined by the liquid displacement method using immiscible solvent (ethyl alcohol) and the true density ρ_T was computed (n=3) according to the following equation:

$$\rho_T = \frac{W_1}{(W_2 + W_1) - W_3} \times SG \quad (1)$$

Where W_1 is the weight of powder, SG is the specific gravity of the solvent, W_2 is the weight of bottle + solvent and W_3 is the weight of bottle + solvent + powder.

Bulk and Tap Density

The bulk and tap density of each material was determined by tapping method (n=3) using Digital tap density apparatus (Electro lab ltd. India).

Flow Properties

Flow Rate

The flow rate (10) of the *R. serpentina* powder and formulations were determined as the ratio of mass (g) to time (s) using a steel funnel with an orifice diameter of 10 mm (n=3).

Kawakita Analysis

Flowability was determined using the Kawakita analysis (11). The method involved pouring a 10 g of powder and formulations into a 50 ml glass measuring cylinde**,** and the bulk volume V_o was accurately measured. Then tapping was started mechanically and the change in volume of the powder column V_N was noted after N no of taps.

The Kawakita equation, which is used for assessing the flow properties of powders, is given by:

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

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 called cohesiveness, C, the degree of volume reduction is calculated from the initial volume V_0 and tapped volume V_N as:

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

Numerical values for constants a and $1/b$ are obtained from the slope, of plots of N/C *versus* number of taps N (N= 10, 30, 100 and 300).

Compaction Studies

Preparation of Compacts

Compacts containing 200 mg of *R. serpentina* were made for powder, granule and direct compression formulation using a Hydraulic pellet press (Kimaya Engineers, India). Compression loads were used in the range of 10 to 95 kg/cm^2. The dimensions (thickness and diameter) and weight uniformity of three compacts were determined. The relative density ρ_T was calculated as the ratio of apparent density ρ_A of the compact to the true density ρ_T, of the powder.

Heckel Equation

The compaction characteristics of the powder were studied with the Heckel (12) equation.

$$\ln \frac{1}{1 - \rho_r} = \mathrm{KP} + A \quad (4)$$

$$\rho_r = \frac{\rho_A}{\rho_T} \quad (5)$$

Where, ρ_T is the relative density of the compact, ρ_A is the apparent density and ρ_T is the true density, P is the applied pressure; K (the slope of the linear portion) is the reciprocal of the yield pressure, P_y, of the material. 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 Equation

For compactability assessment, tensile strength σ_x of the compacts was calculated by the following equation (13) where x is hardness (in kg/cm^2) and d and t are the diameter and thickness of the compacts (in mm), respectively**.**

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

Leuenberger analysis was performed by fitting the data in the following equation (14). A nonlinear plot of tensile strength with respect to product of compaction pressure P and relative density ρ_T was obtained using statistical software (Graph Pad Prism4). 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.

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

Preparation of Tablet

Tablets containing 200 mg of *R. serpentina* were produced by compressing the granules and direct compression formulations using a single station tablet punching machine (Cadmach Machinery Co Pvt. Ltd., Mumbai) equipped with 08 mm circular, flat and plain punches

Table I. Fundamental Powder Characteristics[a]

Materials	Bulk Density (g/cm3)	Tap Density (g/cm^3)	True Density (g/cm^3)	Flow rate (g/s)
Powder (#85/100)	0.270±0.078	0.357±0.062	1.482±0.025	[b]
Direct compression	0.296±0.108	0.384±0.095	1.51 6±0.047	5.64±0.913
Granule	0.286±0.071	0.350±0.072	1.31 3±0.083	4.74±0.729

[a] All values are expressed as mean±SD, n=3
[b] Determination not possible due to blocking of the funnel

Evaluation Tests for Tablets

The prepared tablets of *R. serpentina* root powder both by wet granulation and direct compression were subjected to standard quality control tests for tablets. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet was determined. Hardness was determined by taking six tablets form each formulation using a Digital tablet hardness tester (Electrolab Pvt. Ltd., India) and the average of applied pressure (kg/cm^2) for crushing the tablet was determined. Friability was determined by first weighing ten tablets and placing them in a friability tester (Electrolab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated. Disintegration time for the tablets was determined in 900 ml of distilled water using a Disintegration test apparatus (Electrolab Pvt. Ltd., India).

RESULTS AND DISCUSSION

Quantitative Standards and Drug Content

The root powder was conformed to the quantitative specifications of *R. serpentina* root as per USP. The parameters loss on drying at 100° C to constant weight (10. 5± 1.25%), Acid insoluble ash (1.5±0.40%) and foreign organic matter (2.0±0.8%) were with in the official limits. Average combined content of reserpine and rescinnamine was 0.16± 0.05% calculated as reserpine with reference to the USP reserpine reference standard.

Fundamental Powder Properties

The fundamental flow properties of the *R. serpentina* powder exhibits no flow through funnel, which revealed that it was not up to the theoretical level for processing into tablet dosage form. Flow rate of direct compression formulation and granule revealed a significant improvement in the flowability (Table I). One of the most important factors affecting bulk density of a powder and its flow properties is the interparticulate interaction (15). Desirable micromeritic properties and the optimal presence of water diminish the cohesiveness of the powder, resulting in an increased bulk density for granule and direct compression formulation revealed enhanced flowability (16). Similarly, increased tapped density for granule and direct compression formulation indicated better degree of compactibility as a function of applied pressure (17) (Table I). True density value of powder and direct compression formulation was quite close to each other whereas it was less in case of granules.

Flow Properties

Plots of *N*/*C versus N* (Kawakita plots) for *R. serpentina* Powder and formulations, gave the linear relationship. Kawakita constants indicate the behavior of the powder from the bulk density state to the tap density state. The constants of the Kawakita equation were resolved from the slope and intercept of the line from graphs *N*/*C versus N* (Table II). Granule densified the least (small compressible value) but attained the final packing state most slowly. On the other hand, direct compression formulation densified considerably but achieved the final packing state rather quickly than powder and granule. Lower value of *a* for granule revealed better flowability than direct compression formulation. Whereas, lower value of 1/*b* for direct compression formulation showed that it is less cohesive than granule (18).

Compaction properties

Heckel Analysis

The Heckel plots (Fig. 1) for direct compression formulation and granule showed no linearity at early stages of compression, because of particle rearrangement and the initial fragmentation. Granule showed highest value for die filling in initial stages of rearrangement as indicated by their

Table II. Parameters of Heckel & kawakita analysis

Equations	Parameters	Powder (85/100)	Direct Compression	Granule
Heckel Parameter	Slope ($K\times10^{-2}$)	0.2548	0.3714	0.6423
	Intercept (A)	1.466	2.335	3.710
	Yield Pressure (P_y)	392.5	269.2	155.7
	Coefficient of Determination (r^2)	0.9434	0.9863	0.9097
Kawakita Parameter	Compactibility (a)	0.2516	0.2477	0.2159
	Cohesiveness (1/b)	11.79	9.001	15.33
	Coefficient of Determination (r^2)	0.9992	0.9978	0.9928

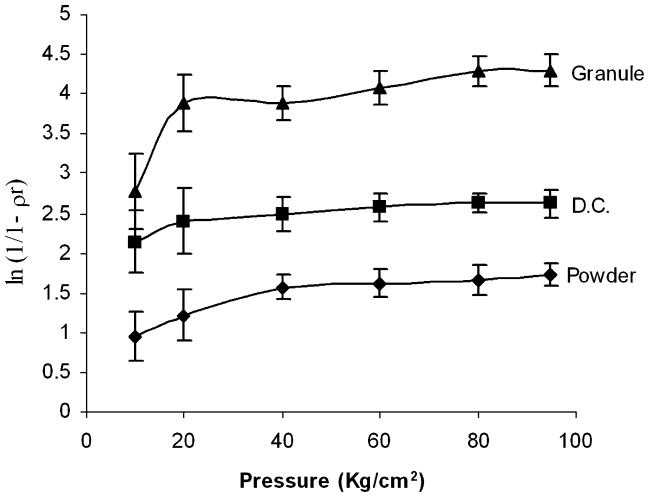

Fig. 1. Heckel plot for *R. serpentina* root powder (*powder*), direct compression formulation (*D.C.*) and wet granulation formulation (*granule*) at various compression pressures (mean±SD, n=3)

intercept *A* values. These features of the later could result to formation of bridges and arches, which could in turn prevent close packing of the particles in the bulk state. Higher value of *A* for granule implies higher degree of fragmentation. At low pressure, the large granule were fractured into small ones, which facilitated the further rearrangement. When the compression pressure was increased, the granule showed plastic deformation (19). Greater slopes indicate a greater degree of plasticity of material.

R. serpentina powder was more resistant to movement, once the initial phase of packing (as a result of die filling) had been completed. This could be attributed to the high cohesive forces likely to be present as a result of its amorphous nature. The mean yield pressure, P_y, values were found to be lower for Granule. The results therefore indicated that granule underwent plastic deformation more easily and rapidly than direct compression formulation. This also confirms that direct compression formulation is somewhat resistant to deformation.

Leuenberger Equation

The compression susceptibility parameter (Fig. 2) for compact formed by direct compression and wet granulation technique indicated that the maximum crushing strength is reached faster at lower pressures of compression as opposed to *R. serpentina* powder. Higher value for $\sigma_{x\ max}$ was observed in case of granule then direct compression formulation. It showed that granule can build a compact with a higher strength than direct compression formulation. Lower value of compression susceptibility for *R. serpentina* Powder demonstrated that maximum tensile strength could be obtained slowly at higher pressure.

Table III. Parameters of Leuenberger Equation[a]

Materials (kg/cm²)	Compression Susceptibility, γ (1/kg/cm²)	Maximum Tensile Strength, $\sigma_{x\ max}$
Powder (#85/100)	0.0190±0.0065	14.77±2.788
Direct compression	0.1652±0.0228	17.79±0.3903
Granule	0.1068±0.0136	29.23±0.7494

[a] All values are expressed as mean±SD, n=3

The parameter $\sigma_{x\max}$ and compression susceptibility allow a characterization of the different materials (20). Low $\sigma_{x\ max}$ value for *R. serpentina* powder showed poor bonding properties. In this regard *R. serpentina* formulations showed moderate bonding properties (Table III). In case of *R. serpentina* powder there is an increasing deviation of the different values for the radial crushing strength when a higher pressure of compression is applied, whereas the crushing strength seem to remain constant independent of the increasing pressure of compression in case of direct compression and wet granulation. This circumstance can be taken as a hint for a capping tendency as with an increasing compression pressure different internal tensions are generated, which can manifest differently when the crushing strength is determined. This tendency could be confirmed by the fact that it was not possible to produce intact tablets at higher pressures of compression because of immediate capping in the die.

Evaluation Tests for Tablets

All the batches of tablets were produced under similar conditions to avoid processing variables. Weight variation for the *R. serpentina* tablets prepared by wet granulation and direct compression method were in the range of 251±08 and 285±11 mg respectively. Hardness of tablets was higher for

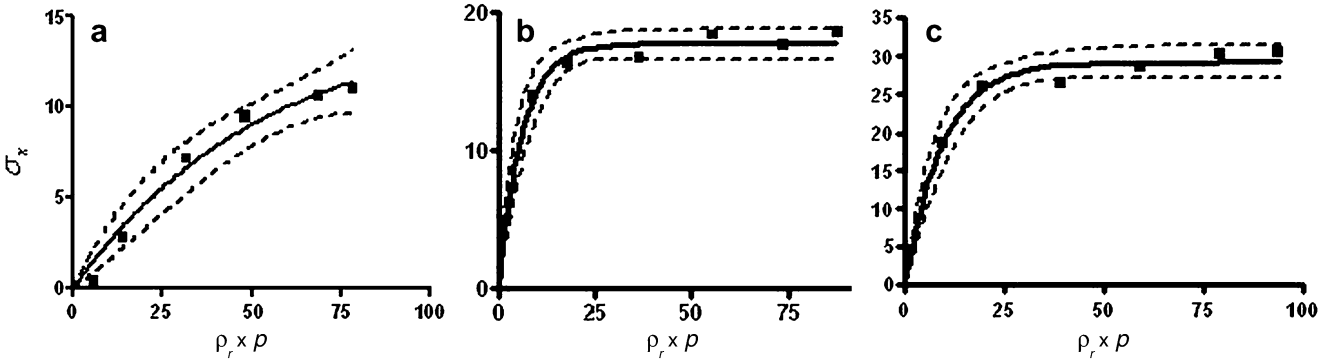

Fig. 2. The radial crushing strength was plotted against the product of the pressure of compression and the relative density. *R. serpentina* root powder **a**, direct compression formulation **b** and granules **c** (mean±SD, n=3)

tablets prepared by wet granulation method (5.2±1.23 kg/cm^2) then the direct compression method (4.8±2.31 kg/cm^2), thickness of tablets prepared by wet granulation and direct compression method was 2.7±0.3 and 2.9±0.4 μm respectively. The percentage friability for tablets prepared by direct compression method (0.75±0.28%) was more than for tablets prepared by wet granulation method (0.46±0.16%). The values of hardness test and percent friability indicated good handling property of the prepared *R. serpentina* root tablets. Disintegration time was 10±2.5 min and 12±1.5 for tablets prepared by direct compression and wet granulation methods respectively.

SUMMARY AND CONCLUSIONS

The results from the Kawakita analysis revealed improved flowability for formulations prepared by direct compression and wet granulation technique. The Heckel plot showed that *R. serpentina* powder is soft in nature, poor in die filling and deforms by initial fragmentation whereas granules and direct compression formulation showed higher degree of plasticity and fragmentation. Leuenberger equation revealed higher value for maximum tensile strength in case of granule then direct compression formulation.

Both wet granulation and direct compression method could be used successfully for developing tablet formulation of *R. serpentina* root powder. But granules showed better flowability, compressibility and compactibility compared to direct compression formulation. Hence, the present study recommends the current needs to generate similar data for different herbal drugs or Ayurvedic formulations, which is highly essential in industrial applications.

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