Design, Development and Rationalization of *Sarpagandha Ghanvati*

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Sarpagandha ghanvati **is a classical Ayurvedic formulation widely prescribed for anxiety and insomnia. It contains *Sarpagandha* (roots of *Rauwolfia serpentina L.* (Benth.) Ex Kurz; Family: Apocyanaceae), *Khurasani ajowan* (*Hyocyamus niger* L.; Family: Solanaceae) seeds, *Jatamansi* (*Nardostachys jatamansi* DC. Family: Valerianaceae) roots and *Pipplamul* (root of *Piper longum* L.; Family: Piperaceae). The objective of this study was to make a comparative evaluation of *Ghanvatis* and tablets of this formulation. Two tablet formulations were prepared; one incorporating only powders of all ingredients; the other with ethanol extracts of the first three ingredients and powder of *Piper longum* root. Similarly, two types of *Sarpagandha ghanvati* pills were prepared; one as per Ayurvedic Formulary of India; the other with ethanol extracts of the first three ingredients and powder of *Piper longum* root. Alcohol extracted 0.22% w/w of total alkaloids as against 0.061% w/w extracted by water. Tablets prepared with powders of all the ingredients had friability more than 3.0% where as those prepared with ethanol extract had very low friability. G*hanvatis*, prepared as per the Ayurvedic formulary, did not show reserpine although other alkaloids were present. They showed less content uniformity and lower drug release. Ethanol extracted reserpine along with other alkaloids. *Ghanvatis* made with the alcoholic extracts exhibited better content uniformity and drug release than the traditional formulation. Tablets prepared with powders or extracts of the ingredients exhibited good content uniformity but the release of alkaloids from the tablets of powders was only 80%. Tablets of the extracts had good content uniformity with 90% release of the total alkaloids. Tablets prepared with alcoholic extracts using 1% polyvinylpyrrolidone as binder and 5% dried starch powder as disintegrating agent confirmed to all the requirements. Thus, the study shows tablets made with the extracts are superior to *Ghanvatis* and powder tablets.**

Key words: Alkaloids, Dissolution, Pills, Reserpine, *Sarpagandha ghanvati*

There has been a sudden increase in awareness of herbal formulations all over the world. However, data on *in vitro* dissolution, content uniformity, in process quality control parameters, and final evaluation of dosage forms that are available for allopathic formulations are not available for majority of herbal products. *Sarpagandha ghanvati* is one of the important Ayurvedic formulations used traditionally in various psychological disorders like insomnia and anxiety[1]. As per Ayurvedic Formulary of India (AFI)[1], it is prepared by using 10 parts of roots of *Rauwolfia serpentina* (*Sarpagandha*), 2 parts of *Hyocyamus niger* seeds (*Khurasani ajowan)*, 1 part of *Nardostachys jatamansi* roots (*Jatamansi*), 1 part of *Cannabis sativa* leaves (*Bhanga*). All these ingredients are extracted in 8 parts water and this extract is concentrated to 1 part to which 1 part of *Piper longum* (Pipali) root powder is added. From the wet mass, *Ghanvatis* (pills) are rolled to get *Ghanvatis* of 375 mg constant weight after drying at 60°. This method of preparation is very complicated and elegance of the pills is very poor. In the present study, ethanol was used in place of water for the extraction of herbs and preparation of the *Ghanvatis.* Tablet formulations of *Sarpagandha ghanvati* with powders as well as extracts were also developed. They were compared with the traditional *Ghanvatis* made as per the classical text and also with the

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Ghanvatis prepared from ethanol extract of the ingredients.

Powders of *Rauwolfia* root, *Hyocyamus* seed, *Jatamansi* root and *Pipali* root were purchased from an established local supplier, L. V. Gandhi and Sons, Ahmedabad, India and passed through a 60 mesh sieve. Other material used in this study such as lactose, microcrystalline cellulose (MCC), starch, gum acacia, polyvinylpyrrolidone (PVP), magnesium stearate and talc (Pharmacopoeial grade) were purchased from Saraiya Chemicals, Ahmedabad, India. Reserpine reference standard was gifted by Vinkem Labs. Private Limited, Kakkalur, Tiruvallur, India. TLC plates (0.2 mm thick) pre-coated with silica gel 60 F 254 (Cat. No. 1.05548, E. Merck, Darmstadt, Germany) were used. Absorbance of the color complex between the alkaloids and the acid dye was measured on a spectrophotometer (Elico, Hyderabad, India). Distilled water was used throughout the study and rectified spirit was used for the preparation of ethanol extracts. All chemicals used for the analysis were of analytical reagent grade.

Various methods have been attempted to extract the alkaloids from *R. serpentina* powder. Simple cold maceration overnight employing water/chloroform/ethanol/ethanol plus hydrochloric acid (1.0% v/v) was attempted and the total alkaloids extracted were assayed. Similarly, the drug powder was refluxed in alcohol plus hydrochloric acid (1.0% v/v) and the extracted alkaloids quantified. The extracts obtained in the above processes were spotted on a Silica gel GF 254 pre-coated aluminum plate and run in a solvent system consisting of toluene:ethyl acetate: diethyl amine (7:2:1) along with standard reserpine. The spots were visualized by spraying with modified Dragendorff's reagent to note the number of alkaloid spots and their R_f values.

Total alkaloids of *R. serpentine* in the formulations have been estimated using a method reported by Pundarikakshudu *et al*.[2]. This method is based on the formation of an ion pair complex between alkaloids and methyl orange at pH 4.5, which can be extracted in to chloroform, followed by release of the dye from the chloroform in to hydrochloric acid. Standard solution of reserpine (1 mg/ml) was prepared by dissolving 100 mg reserpine in 10 ml of chloroform and making the volume to 100 ml with methanol. Ten millilitres each of 5, 10, 15, 20, 25, 30 and 35 μg/ml concentration of reserpine was made by proper dilutions of standard solution with chloroform. It was taken in to a separating funnel, 5 ml of acetate buffer (pH 4.5) and 3 ml of 0.05% methyl orange solutions were added and the contents were shaken well. The complex formed was extracted thrice with chloroform (3×10 ml). The pooled chloroform extracts containing the complex were transferred to another separating funnel containing 25 ml of 1 M hydrochloric acid. The dye liberated in to hydrochloric acid from the complex was measured against a blank at 530 nm. Blank was prepared by the same method described above without addition of reserpine. The absorbance values were plotted against their respective concentrations of reserpine to obtain a linearity curve.

For the extraction of alkaloids from the formulations, weighed quantities of the dosage forms were taken, moistened with 10% ammonia (2 ml), dried and refluxed with chloroform (50 ml) for 1 h. This mixture was filtered, filtrate concentrated and volume was adjusted to 25 ml with chloroform. Measured volume (0.5 ml) of this extract was taken and diluted to 10 ml with chloroform in a volumetric flask. This was treated with reagents as described above. The amount of total alkaloids from the dosage forms were calculated from the calibration curve and represented as reserpine. All experiments were carried out in triplicates.

*Sarpagandha ghanvati*s were prepared by blending 11 part of *Rauwolfia serpentina*, 2 part of *Hyocyamus niger*, 1 part *Nardostachys jatamansi*, macerating and shaking occasionally for 24 h in water, warming, filtering and concentrating the extracts on water bath to 1 part to which 1 part of *Piper longum* root powder was added to make pills of 375 mg dry weight. For the preparation of *Sarpagandha ghanvati* of alcoholic extract (SGAE), 100 g powder of each drug was extracted separately in 95% ethanol with Soxhlet apparatus up to complete extraction of the drug. The extracts were filtered and concentrated on a water bath at 50±1° till a gummy mass was obtained. *Sarpagandha ghanvatis* of alcoholic extracts (SGAE) were prepared by mixing amount of extracts representing 11 part *Rauwolfia* root, 2 part *Hyocyamus* seed, and 1 part *Jatamansi* root. One part of this mixed extracts is added to 1 part of *Pipali* root powder. This was rolled into pills and dried at 50° to get pills of 375 mg.

Powders of *Rauwolfia* root (11 parts), *Hyocyamus* seed (2 parts), *Jatamansi* root (1 part) and *Pipali* root (14 parts) were blended with different diluents like lactose, MCC and starch in the ratio of 1:0.5. Granules were prepared using PVP (3, 5 and 7%) in isopropyl alcohol, starch paste (5, 7 and 10%) and starch paste (5%) with gum acacia (2%) as binders and dried starch (5%) as a disintegrating agent. Granules were lubricated with 1% magnesium stearate, and 2% talc. Granules were compressed using a Dhiman made single stroke multi punch tablet press with round punches, to give tablets of an average weight of 500 mg.

Tablets of SGAE were prepared by wet granulation technique. The extracts and *pippali* powder were mixed as described for the extract *Ghanvatis*. Since the extract is semisolid, less amount of binder would be necessary to prepare tablets. Diluent was selected on the basis of the results of previous study. PVP (1, 2 and 3%) or starch paste (3, 5 and 7%) and dried starch (5%) were added as binder and disintegrating agent, respectively. Granules were compressed using a Dhiman made single stroke multi punch tablet press with round punches. The tablets had an average weight of 300 mg.

Ghanvatis made as per API were analyzed for the presence of reserpine by thin layer chromatography using mobile phase toluene:ethyl acetate: diethylamine (7:2:1). They were also evaluated for total alkaloids, crushing strength, disintegration time and release of the total alkaloids.

Tablets made up of SGAE and powder ingredients of *Sarpagandha ghanvati* were evaluated for pre formulation and post formulation parameters. Angle of repose, Carr's index, Hausner's ratio, crushing strength, friability and disintegrating time were measured as per standard methods[3]. The best tablet formulation of SGAE/powders and *Ghanvatis* made from alcoholic/water extracts were subjected to *in vitro* dissolution study in USP 24 dissolution apparatus type II at 37±0.5° and at 100 rpm using simulated gastric fluid (pH 1.2) as dissolution medium. The dissolution medium was filtered through a Whatman filter paper and basified with ammonia to pH 9.0. The liberated alkaloids are extracted into chloroform (3×15 ml), chloroform extracts pooled, dried over anhydrous sodium sulphate and color developed as described above with acid dye reagent.

In *Sarpagandha ghanvati, Rauwolfia* (*Sarpagandha*) is the main ingredient responsible for the therapeutic activity. About 30 alkaloids are reported to be present in *Rauwolfia* of which reserpine is the main alkaloid. Hence, we evaluated the formulations and raw material in terms of this alkaloid. Water did not extract reserpine but only some alkaloids other than reserpine were extracted. Ethanol and chloroform were found to be equally efficient, which extracted 0.22% w/w of total alkaloids including reserpine as the main alkaloid. The total alkaloids extracted in water were only 0.061% w/w. There was around 50% increase in efficiency of alkaloid extraction when acidic alcohol was used instead of only ethanol (Table 1). Starch gave better compressibility and flow properties as compared to other diluents (Table 2). Starch paste and starch paste plus gum acacia did not give satisfactory results. As shown in Table 3, tablets prepared with starch paste and starch paste plus gum acacia had very high friability (1.7–5.2%) and low crushing strength (2.4–2.8 kgf). Polyvinyl pyrrolidone (PVP) at 3 and 5% showed better tablet hardness and low disintegration time, but the friability was more than 3%. Tablets of alcoholic extracts were prepared using wet granulation method. All the

TABLE 1: TOTAL ALKALOID EXTRACTION OF *RAUWOLFIA SERPENTINA*

Method of extraction	Total *Rauwolfia* alkaloids calculated as reserpine* (% w/w)
Maceration with chloroform	0.2120±0.049
Maceration with ethanol	0.2216±0.017
Maceration with ethanol+HCl (1% V/V)	0.3133±0.019
Ethanol+hydrochloric acid (1% V/V) reflux	0.345±0.080
Maceration with water	0.0610±0.009

*Mean of three readings

TABLE 2: EFFECT OF DILUENTS ON DERIVED PROPERTIES OF *SARPAGANDHA GHANVATI* PREPARED WITH POWDERS OR EXTRACTS

Parameter	Diluents					
	Starch		Lactose		MCC	
	Powder	Extract	Powder	Extract	Powder	Extract
Bulk density	0.56	0.61	0.46	0.52	0.28	0.34
Tapped density	0.71	0.76	0.66	0.70	0.56	0.58
Carr's index	21.12	19.73	30.0	25.7	50.0	41.8
Hausners' ratio	1.26	1.24	1.43	1.34	2.00	1.70
Angle of repose (θ)	37	36	36	36	42	40

MCC: microcrystalline cellulose

TABLE 3: EFFECT OF BINDERS ON DERIVED PROPERTIES OF *SARPAGANDHA GHANVATI* TABLETS PREPARED WITH POWDER INGREDIENTS*

Parameter	Batches						
	WP1	WP2	WP3	WP4	WP5	WP6	WP7
PVP (% w/w)	3	5	7	-	-	-	-
Starch paste+gum acacia (% w/w)	-	-	-	5+2	-	-	-
Starch paste (% w/w)	-	-	-	-	5	7	10
Carr's index	20.60	21.20	28.40	27.10	23.50	22.60	20.25
Hausners' ratio	1.14	1.10	1.38	1.26	1.15	1.17	1.11
Angle of repose (θ)	27	30	32	38	28	29	30
Friability (% w/w)	3.5	3.1	3.1	3.6	5.2	4.6	1.7
Crushing strength (kgf)	6.2	8.8	9.0	4.2	3.4	4.8	5.8
Disintegration time (min)	1.5	3.5	7.0	5.5	1.0	3.0	4.0

*Weight of each tablet is 500 mg. PVP: polyvinylpyrrolidone

TABLE 4: TABLET FORMULATION OF *SARPAGANDHA GHANVATI* PREPARED WITH EXTRACTS

Parameters	Batches					
	WE1	WE2	WE3	WE4	WE5	WE6
PVP (%w/w)	1	2	3	-	-	-
Starch paste (%w/w)	-	-	-	3	5	7
Dried starch powder (%w/w)	5	5	5	5	5	5
Crushing strength (kgf)	5.8	6.9	8.5	4.4	4.0	4.6
Friability (%)	0.12	0.06	0.03	Very high	Very high	Very high
Disintegration time (min)	8	13.5	15.0	2.5	2	1

Weight of each tablet is 300 mg. PVP: polyvinylpyrrolidone

TABLE 5: COMPARISON OF FORMULATION PARAMETERS OF *SARPAGANDHA GHANVATI*

Parameters	*Ghanvatis* prepared from alcoholic extracts	*Ghanvatis* prepared as per API
Crushing strength (kgf)	8	6.8
Friability (%)	0.00	0.00
Disintegration time (min)	45	18

API: Ayurvedic Pharmacopoeia of India

TABLE 6: CONTENT AND PERCENT RELEASE OF TOTAL *RAUWOLFIA SERPENTINA* ALKALOIDS FROM DIFFERENT FORMULATIONS

Formulation	Total alkaloids (mg) per tablet/pill*		Percentage release of total alkaloids
	Present	Released	
Batch-WP2	0.65±0.118	0.564±0.111	80
Batch-WE1	1.20±0.015	1.080±0.045	90
Ghanvati of alcoholic extracts	1.20±0.048	0.850±0.075	71
Ghanvati as per API	0.35±0.042	0.196±0.061	56

*Mean of three values. API: Ayurvedic Pharmacopoeia of India

batches showed very good crushing strength at low concentration of binders. PVP gave better binding and hardness (6.0–8.5 kgf) in tablets made with ingredient extracts. Friabililty in these tablets was negligible. When starch paste was used in place of PVP, hardness decreased and friability increased (Table 4). The *Ghanvatis* of the classical and modified methods had zero friability and 7.0–8.0 kgf crushing strength respectively. But *Ghanvatis* of the alcohol extracts had very high disintegration time of 45 min as against 18 min of the classical formulation (Table 5). Tablets of the powders contained 0.65 mg of total alkaloids per tablet while those prepared with the ethanol extracts contained 1.20 mg of the total alkaloids. *Ghanvatis* prepared with the alcoholic extract had 1.2 mg of total alkaloids per pill while those prepared with the traditional process had only 0.33 mg. Batches WP-2 and WE1 with less disintegration time were selected for dissolution study. Tablets made with the ethanol extract released 90% of the alkaloids whereas powder tablets released 80% of the alkaloids. The release of alkaloids from the pills of the extracts was 71%. Traditional pills released only 56% of the alkaloids (Table 6).

The high disintegration time of the pills is due to non-inclusion of any disintegrating agent like starch powder which has been used in the tablet formulation. Since the total alkaloids have to get released within the 45 min of dissolution study from the powders, there was less release as compared to the release of the alkaloids from the extracts. The low content of the alkaloids in the traditional pills is expected as water was found to be unsuitable for the extraction of the alkaloids. From our experience, we found that it is very difficult to prepare pills of uniform content and it is not possible to predict the exact quantities of the alkaloids in the pills. Ethanol extracted all the alkaloids including reserpine and also gave consistent content uniformity and drug release.

There has been a lot of renewed interest in the herbal and Ayurvedic products. Data on process optimization, evaluation of the product for content uniformity, dissolution and others, is not available for many of the classical formulations. Momin *et al*. and Momin and Pundarikakshudu[4,5] reported the superior nature of triphala tablets over the classical triphala powder and also applied the current understanding of targeted drug delivery systems to the development of colon targeted tablets of triphala. Their studies clearly showed the advantages of the modern dosage forms over the

classical formulations especially in administration, uniformity, elegance and convenience of manufacturing.

Classical method of preparation of *Sarpagandha ghanvati* involves concentration of water extract to 1/8 of the volume. Water did not extract the alkaloids effectively and it takes lot of time to concentrate water in large volumes. Hence, tablets prepared with extracts in our studies are superior to the classical pills as they can be manufactured in large scale with ease, evaluated for all the process parameters, and ensure elegant, uniform dosage form of this classical formulation.

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There are no conflicts of interest.

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