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## Development of Standardized Formulation of mono herbal (250mg) Capsule

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**ABSTRACT**

The aim of study is to develop the oral and stable herbal dosage of *Vitex negundo* Linn. fruit. Powder were formulated in 250 mg capsule and phyto-pharmaceutical studies of *Vitex* fruits were carried out according to the Pharmacopoeial standards. The pre formulation arrangement was characterized for sieving, granulation, flow ability of powder, angle of repose, porosity of powder. The post formulation studies such as weight variations, and disintegration, dissolution and stability under various storage conditions were also performed. Pre-formulation analysis showed that the flow property of powder is excellent, having the mean value of angle of repose as  $<30^\circ$ . The Carr's compressibility index CI and HR were found to be 15.5 and 1.182 respectively. The disintegration time was 6-13 min and dissolution also occurred which were within the limit. For the stability studies of capsules were exposed to environmental factors, light temperature and humidity and found stable under provided conditions.

**Keywords:** *Vitex negundo*, Herbal pharmaceutical dosage, Phyto-pharmaceutical.

**1. Introduction**

Medicinal plants are the local heritage with global importance. World is endowed with a rich wealth of medicinal plants. Herbs have always been the principal form of medicine in Asia especially in Pakistan, China and India; presently they are becoming more popular throughout the developed world. As people are strive to stay healthy in the face of chronic stress and pollution, and to treat illness with medicines that work in concert with the body's own defenses, herbs provide the starting material for isolation or synthesis of conventional drugs<sup>[1]</sup>. During the past decade, a dramatic increase in exports of medicinal plants attests to worldwide interest in these products as well as in traditional health systems. Instead of that the remedies provided either by allopathic, by homeopathic or herbal, the sole objective of all types of medicine is to restore the patient to good health. Therefore, now herbal drugs are formulated in primary dosage form for the ease and acceptability of patients<sup>[2, 3]</sup>. In the present study we were formulated the single dried fruit in a capsule and evaluate the pharmaceutical quality of capsule dosage.

*Vitex* genus is the most important member of *Verbenaceae* family and consists of 2500 species all over the world. From the literature it is revealed that the most popular three species *Vitex trifolia*, *Vitex negundo* and *Vitex agnus-castus* which is comprise of two varieties *agnuscastus* and *pseudo-negundo* of this genus are available in Pakistan and used in various ailments<sup>[4]</sup>. This genus has revealed marvelous activity in various gynecological problems along with analgesic, anti-inflammatory, antiviral, antifungal, and antibacterial activity<sup>[5, 6, 7]</sup>. *Vitex negundo* has various essential oils including  $\delta$ -guaiene; guaia-3,7-dienecaryophyllene epoxide; ethyl-hexadecenoate;  $\alpha$ -selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol;  $\beta$ -selinene;  $\alpha$ -cedrene; germacrene D; hexadecanoic acid; p-cymene and valencene, isolated from its fruit, flowers and fresh leaves<sup>[8, 9]</sup>. This therapeutic plant is used in Pakistan in chest pain, backache, antiallergent agent, and gum and skin disease and also as tooth brush<sup>[10, 11, 12]</sup>. No utilization of fruits of *V. negundo* in gynaecological disorders reported till now, this is first time we formulated as a single herb in capsule dosage to treat the feminine disorders.

## 2. Material and Method

### 2.1 Plant material

The fruits of *Vitex negundo* Linn. (13 kg) were purchased from local herbal market (Jodia bazaar, Karachi-74000) and authenticated by Prof. Dr. Ghazala H. Rizwani, Dean Faculty of Pharmacy. A voucher specimen (0041) had been deposited at the Herbarium of Department of Pharmacognosy, faculty of Pharmacy University of Karachi.

### 2.2 Cleansing and drying

The fruits (*Vitex negundo*) were washed with fast flow clean tap water quickly transferred into large sieve and then spread them on filter paper (Whatman No. 1) to absorb excesses water, then dried the fruits in oven at 35-45 °C.

### 2.3 Macroscopic Evaluation

Plants first examined by sensory organs (touch, smell/odour, slight, taste fracture). This method was used for describing the organoleptic features of the drugs.

### 2.4 Grinding

After drying the fruits were ground into coarse powder form with the help of electric grinder (West Point automatic series TSK-333 France). The color of powder drug was dark brown and has acrid taste with typical herbal odor.

## 3. Formulation of oral dosage form

Formulation of solid dosage form either in a tablet or capsule required a preformulation and formulation studies according to the pharmacopoeial standard to achieved standardized products<sup>[13, 14]</sup>.

### 3.1 Pre-formulation study

#### 3.1.1 Sieving and Granulation

Sieving is widely used technique for sizing granular and powdered material<sup>[15]</sup>. Powdered material was passed through different sieves (40 and 60) to make a coarse particle size.

#### 3.1.2 Flowability of powder

The flow ability of powder is useful in clinical application of drug uniformity when it is used as dosage form. It can be performed by various methods in the present study we were used two methods to evaluate the flow properties such as angle of repose and porosity of powder.

##### a) Angel of Response of Powder

The cohesiveness and non-cohesiveness of the powdered fruits (*V. negundo* Linn.) has been done by fixed base cone method. 3 g of powdered drug was used to measure the angle of repose and calculate by the following equation:

$$\theta = \tan^{-1} \frac{2h}{D}$$

Where h = height of powder  
D = diameter of Petri-dish

##### b) Porosity of Powder

Powder porosity is another method which is useful in characterization of packing geometry and linked to the bulk density of the powder. The percent porosity of powdered fruits was calculated as:

$$\% \varepsilon = \frac{V_b - V_p}{V_b}$$

Where  $V_b$  = bulk volume  
 $V_p$  = Packed volume

##### c) Bulk density and Tap density

Bulk and tapped densities were determined by simple filled cylinder tapping method. A 100 ml graduated cylinder was filled two third with *Vitex* powder, tapped on plane surface and observed the change in volume (tapped volume). Both densities were calculated by using following formulae:

$$\rho_{\text{bulk}} = m / V_b \quad \text{and} \quad \rho_{\text{tapped}} = m / V_p$$

Where m is weight of powdered drug.

##### d) Compressibility indices

The bulk and tapped densities were used to calculate the compressibility indices (Carr's index and Hausner ratio) which provide the flow properties and compressibility of powders.

$$\% \text{ Carr's Index} = \frac{\rho_{\text{tap}} - \rho_{\text{bulk}}}{\rho_{\text{tap}}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{\text{tap}}}{\rho_{\text{bulk}}}$$

Where  $\rho_{\text{tap}}$  = tap density and  $\rho_{\text{bulk}}$  = bulk density.

## 3.2 Quality control parameters

The capsule dosage form is extremely versatile due to ease of swallowing and greater patient acceptance<sup>16</sup>. We were filled the powdered fruits of *V. negundo* in 250 mg capsule (size no. 0). For the analysis and evaluation of the quality of mono herbal capsule, a number of different pharmacopoeial and non-pharmacopoeial physicochemical tests were performed.

### 3.2.1 Weight variation

This weight variation requirement measures the variability in the amount of powder contained in each capsule. The capsule shall not be less than 90% and not more than 110% of the theoretically calculated weight of each unit. The average weight of capsule along with length and diameter was determined by weighing randomly selected 20 capsules on electronic balance (Mettler Toledo B204-S) and vernier caliper respectively.

### 3.2.2 Disintegration

The efficacy of a drug can be dependent on the rate which the tablet or capsule disintegrates in the patient's gastrointestinal tract. The disintegration test is a measure of the time required under a given set of conditions for six randomly selected capsules to disintegrate into particles which will pass through a 10 mesh screen with in a disintegration assembly at maintained temperature 37 °C±2 °C (Varian Model VR100 35-1200). Generally, the test is useful as a quality assurance tool for conventional dosage forms.

### 3.2.3 Dissolution

Dissolution is considered as a tool for predicting rate of absorption and bioavailability in some cases, replacing clinical studies to determine bioequivalence of drug. We were added six capsules in the basket type dissolution apparatus (Vankel VK700) containing

distilled water as a dissolution media. The speed was set on 50 rpm for 1 hour and the sample was drawn at every 10 minutes and the amount of dissolved active ingredient in the solution was calculated as percentage dissolved in 1 hour.

### 3.2.4. Stability

Pharmaceutical products are generally studied for stability profile at accelerated temperature, humidity and also at different intensities of light. The studies were performed to determine the physical, chemical, and therapeutic changes occurring in the monoherbal capsule by extrinsic factors [17, 18].

#### (a) Light

Sample was stored in different intensities of light i.e. sunrays, fluorescent (tube) light, UV and infrared light for detection of degradation of powder material, then the fruits powder was subjected to TLC chromatography on silica gel fluorescence (254 nm) plate in a suitable solvent system EtOAc: MeOH: H<sub>2</sub>O (7 ml: 10 ml: 0.1 ml) to monitor the stability of 250 mg monoherbal capsule containing fruits powder of *Vitex*.

#### (b) Temperature

The effect of temperature on the stability of monoherbal capsule was checked by keeping all the capsule at different temperatures i.e. ambient, 35 °C, 50 °C, 55 °C, 65 °C for 30 minutes, 1, 3, and 6 hours.

#### (c) Humidity

The effect of humidity on the stability of capsule was checked by

keeping the entire capsule at four different humidity percentage i.e. 30%, 50%, 70% and 90%.

## 4. Results

### 4.1 Macroscopic Evaluation

Plant drugs identification is a very crucial problem in the utilization of herbal drugs especially in dried form whenever they are used either as drug in any ailment or as raw material in pharmaceutical. The organoleptic features of the dried fruit of *V. negundo* were as follows:

Texture	→	Rough
External marking	→	slightly wrinkled and glossy, thin scar.
Internal marking	→	Shiny, tetra chamber fruit, very prominent four septums present.
Fracture	→	Hard
Shape	→	a globose, ovoid or obovoid
Size	→	1.2-2 mm
Color	→	Blackish brown
Taste	→	Acrid

### 4.2 Pre-Formulation Evaluation:

#### 4.2.1 Flow Property of Powder

Powder flow is a key requirement for pharmaceutical manufacturing process. The results of angle of repose, porosity, Carr's index and Hausner's ratio of powdered fruit material prior to capsule filling were tabulated in Table 1 and 2.

**Table1:** Measurement of angle of repose of fruits powder of *Vitex negundo* Linn.

Run Number	Height of Conical Powder	Radius of Petri dish (cm)	Angle of Repose $\theta = \tan^{-1} \frac{2h}{D}$
1	1.1	3.7	16.54
2	1.3	3.7	19.34
3	1.2	3.7	17.95
Mean	1.2	3.7	17.9 <sup>o</sup>
± SD	0.1	---	1.4

**Table2:** Measurement of porosity, compressibility index and Hausner's ratio of fruits powder of *V. negundo* Linn

S. No.	Bulk volume of powder (V <sub>b</sub> ml)	Volume occupied by Powder after 100 tapping (V <sub>p</sub> ml)	$\epsilon = \frac{V_b - V_p}{V_b}$	Compressibility index	Hausner ratio $\frac{V_b}{V_p}$
1	26.0	22.1	0.15	15	1.176
2	21.1	21.9	0.161	16.1	1.19
3	26.0	22.0	0.154	15.4	1.18
Mean	-----	-----	0.155	15.5	1.182
± SD	-----	-----	0.0056	0.557	0.007

### 4.3 Quality control evaluation:

#### 4.3.1 Weight variation

The physiochemical feature of the monoherbal capsule was shown in Figure-1. The powdered fruit material of *Vitex negundo* Linn was filled in capsule (size=zero (0)) by manual method and weight uniformity checked along with diameter and length of the capsule and was found the average weight of capsule 250 mg±7.5%.

#### 4.3.2 Disintegration and dissolution:

Table 3 showed that the disintegration time was within 9-13 minutes for all six capsules and were fulfill the requirement of standard dissolution profile as shown in Figure-2. The releasing pattern of capsule revealed that they were dissolved up to 90% within 30 minutes.

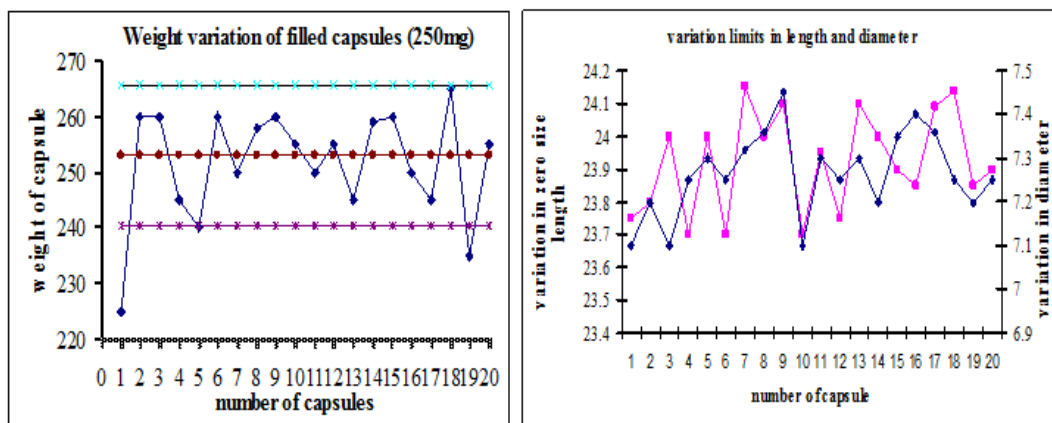


Fig 1: Measurement Of Weight Variation, Diameter and Length of monoherbal capsule (250 mg)

Table 3: Disintegration time of monoherbal Capsules (min)

Capsules	1	2	3	4	5	6	Mean	+ SD
Time (min)	6 min	13 min	9 min	11 min	12 min	8 min	9.83 min	2.64

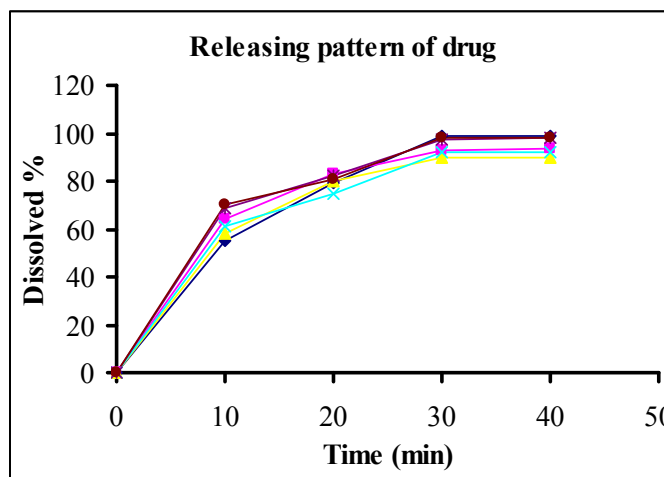


Fig 2: Dissolution profile of monoherbal capsule

4.3.3 Stability

The stability parameters were analyzed for 30 minutes, 1, 3 and 6 hours of storage at accelerated conditions of temperature, light and humidity were found to be comparable. It was indicating that there

gross physical characteristics does not produce any significant change, observation have been tabulated in table 4, 5 and 6 for three Stability parameters

Table 4: Effect of different intensities of lights on monoherbal capsules (250 mg)

Light Source	Sun light				Fluorescence Tube light				UV Light				Infra-Red (IR) Lamp Light			
	1/2	1	3	6	1/2	1	3	6	1/2	1	3	6	1/2	1	3	6
250mg monoherbal capsule	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+

(-) No change, (+) Degradation

Table 5: Stability test of monoherbal Capsule (250mg) at different Temperature

Storage condition	Testing condition	Time Duration (hours)				Result
		1/2	1	3	6	
Ambient	30 °C	—	—	—	—	No change during 6 hours
Warm (30-40 °C)	35 °C	—	—	—	—	No change during 6 hours
Accelerated	50 °C	—	—	—	—	No change during 6 hours
Accelerated	55 °C	—	—	—	+	Degradation start after 4 hours
Accelerated	65 °C	—	—	+	+	Degradation start after 2 hours

(-) No change, (+) Degradation start

**Table 6:** Stability of monoherbal Capsule (250 mg) at different Humidity with respect to different Temperature

Temperature	30% Humidity	50% Humidity	70% Humidity	90% Humidity
30%	-	-	-	-
35%	-	-	-	-
55%	-	-	+	++
65%	-	-	++	+++

(+) Degradation

(-) No Change

## 5. Discussion

Various types of herbal medicines have been used as curative agents in different parts of the world <sup>[19]</sup>. Drugs derived from traditional herbs may have possible therapeutic relevance in the treatment of illness <sup>[20]</sup>.

In the present research work *Vitex negundo* Linn fruits were used for the oral monoherbal 250 mg capsule. First it was formulated and then evaluated for quality herbal product which is very important irrespective of their medicinal content and therapeutic states therefore the pre-formulation and formulation studies of the formulated monoherbal capsule were evaluated. The organoleptic evaluation of fruits gives the authentication to the drug which is being utilized for the formulation.

Preformulation parameters including angle of repose (a traditional characterization method for pharmaceutical powder flow), porosity (packing geometry), Carr's index and Hausner's ratio (a measure of the interparticulate friction) are useful tools in the development of new formulation. A value of  $<30^\circ$  indicates 'excellent' flow whereas  $>56^\circ$  indicates 'very poor' flow. Based on this, the flow was rated as 'excellent' (Table-1). The CI and HR were found to be 15.5 and 1.182 Lower CI or lower Hausner ratios of a material indicates better flow properties than higher ones. A Carr's CI of  $<10$  or HR of  $<1.11$  is considered 'excellent' flow whereas  $CI > 38$  or  $HR > 1.60$  is considered 'very very poor' flow <sup>[21, 22]</sup>. Based on the results obtained (Table-2) flow of *Vitex negundo* fruit powder was rated as 'good'. Good flow of powder help to avoid the extensive costs and time involved in unloading powders that will not flow out of storage containers. As well as help to achieve the best formulation and improve the quality and consistency of the product.

*Vitex negundo* Linn was approved as quality drug when undergone by phytopharmaceutical evaluation according to the pharmacopoeial standards. 250 mg monoherbal capsules disintegrated in meantime  $9.88 \pm 2.64$  minutes and in vitro condition and we determined the release of a drug from solid dosage format which the substance dissolved in the fluid of gastrointestinal tract. Fig. 2 indicates that all of six capsules dissolved equal to 90% in 30 minutes and this releasing pattern of drug from their capsule shell in-vitro help in predicting the releasing sequence in-vivo that developing a tool for bioavailability of drug, as well as in some cases, replacing clinical studies to determine bioequivalence. In light of the phytopharmaceutical studies of the capsule of *Vitex negundo* Linn fruit powder was found almost stable.

Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as light, temperature, and relative humidity etc. which are required to demonstrate that a pharmaceutical product meets its acceptance criteria throughout its shelf life and to gain regulatory approval for commercialization<sup>17</sup>. The result showed in Table-4 sunlight no degradation was observed after 30 minutes, 1, 3, 6 hours of exposure and the product remain unchanged while in fluorescence (tube light) and, UV lamp also shown no degradation whereas exposure to the IR Lamp revealed

the degradation of powder after 5 hours. Effect of temperature was observed and found remain unchanged at ambient temperature to  $50^\circ\text{C}$  up to 6 hours, but only at accelerated temperature after 4 hours slight changing in powder color was observed (Table-5). In humidity studies of powdered sample of *Vitex negundo* Linn. at 30%, 70% and 90% sample powdered was found unchanged while slight gradual degradation was seen at 70% and 90% humidity (Table-6).

## 6. Conclusion

Above study indicated that the single unit oral dosage form of fruits of *Vitex negundo* Linn. formulated in a capsule 250 mg. The phytopharmaceutical evaluation showed that the pre formulation and formulation studies of fruits was stable under required conditions like temperature, light and humidity. However real time revisions on stability are ongoing to confirm these findings.

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