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Research Article

Development & Evaluation Of Polyherbal Granules Filled Hard Gelatin Capsules Containing Clitoria Ternatea & Vitex Agnus Castus For Menopausal Symptom Management

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ABSTRACT

Women's quality of life is impacted by menopause, which is linked to a number of psychological and physical ailments brought on by hormonal imbalance. The goal of the current study was to create and assess hard gelatin capsules filled with polyherbal granules including Vitex agnus-castus and Clitoria ternatea for the treatment of menopausal symptoms. These herbs were chosen for their hormone-regulating, adaptogenic, antioxidant, and anxiolytic qualities. To enhance flow characteristics and capsule filling efficiency, the formulation was made utilising the wet granulation method with the right excipients. Pre-compression characteristics, including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio, were assessed for the produced granules. In accordance with pharmacopeial requirements, the filled capsules were additionally assessed for weight variation, disintegration time, content consistency, and stability studies. The optimised formulation demonstrated acceptable stability, homogeneity, appropriate disintegration, and satisfactory flow characteristics. According to the study, the created polyherbal capsule formulation may enhance patient compliance and quality of life while acting as a safe and efficient herbal substitute for the treatment of menopausal symptoms. To verify its therapeutic efficacy and safety, more clinical research is advised.

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INTRODUCTION

1.1. Menopause

Menopause is a natural physiological condition in women, usually occurring between 45–55 years of

age, characterized by the permanent cessation of menstruation due to decreased ovarian function. This leads to a decline in estrogen and progesterone hormone levels.

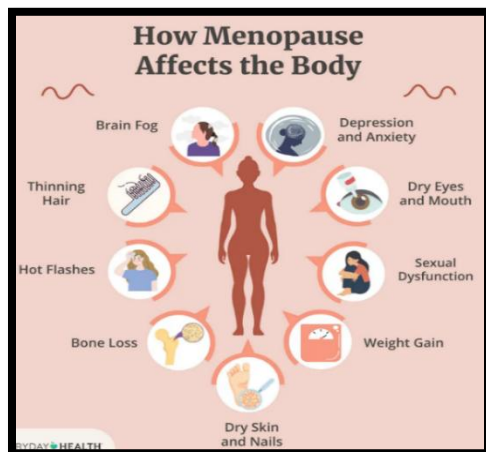


Fig 1: Menopause symptoms

Hormone Replacement Therapy (HRT) is commonly used to manage menopausal symptoms. However, long-term use of HRT may lead to side effects such as increased risk of cardiovascular diseases and breast cancer. Therefore, there is a growing interest in combining synthetic drugs with herbal ingredients for safer and more effective therapy. Tibolone is widely used for managing menopausal symptoms due to its estrogenic, progestogenic, & androgenic activity. It helps in relieving vasomotor symptoms and prevents bone loss. [1]

1.1.1. Prevalence of Menopause

Menopause is a natural biological process characterized by the permanent cessation of menstruation due to the loss of ovarian follicular activity. It generally occurs between the ages of 45 and 55 years, with the average age being approximately 50 years worldwide. In India, menopause commonly occurs slightly earlier, around

46–48 years of age. The prevalence of menopause is increasing globally because of improved life expectancy and better healthcare facilities. According to epidemiological studies, millions of women enter menopause every year, and postmenopausal women constitute a significant proportion of the female population worldwide.[2] It is estimated that women spend nearly one-third of their lives in the postmenopausal phase. Various menopausal symptoms are highly prevalent among women, including hot flashes, night sweats, mood changes, sleep disturbances, osteoporosis, and cardiovascular complications. The prevalence and severity of menopausal symptoms vary depending on genetic, environmental, nutritional, and socioeconomic factors. Vasomotor symptoms such as hot flashes are reported in nearly 50–80% of menopausal women. Osteoporosis and cardiovascular diseases are also more common after menopause due to oestrogen deficiency. Increasing awareness regarding menopause and its management is important because the growing



population of postmenopausal women represents a major public health concern.^[3,4,5]

1.1.2 Causes of Menopause^[6,7]

Menopause occurs mainly due to the natural decline in ovarian function and depletion of ovarian follicles with advancing age. As the ovaries lose their ability to produce oestrogen and progesterone hormones, menstrual cycles gradually become irregular and eventually cease permanently. The causes of menopause can be classified into natural, premature, surgical, and induced menopause.

i. Natural Menopause

Natural menopause occurs as a part of the normal aging process in women, usually between 45–55 years of age. It results from gradual depletion of ovarian follicles and reduced secretion of estrogen and progesterone hormones.

ii. Premature Menopause

Premature menopause occurs before the age of 40 years. It may be caused by:

- Genetic abnormalities
- Autoimmune disorders
- Ovarian failure
- Severe infections
- Metabolic disorders

iii. Surgical Menopause

Surgical menopause occurs due to surgical removal of both ovaries (bilateral oophorectomy). It may also occur after hysterectomy if ovarian blood supply is affected. Symptoms are usually sudden and more severe because hormone levels decline abruptly.

iv. Induced Menopause

Induced menopause may occur due to:

- Chemotherapy
- Radiotherapy
- Anticancer drugs
- Certain hormonal treatments

These treatments damage ovarian tissue and reduce hormone production.

v. Lifestyle and Environmental Factors

Certain factors may contribute to early menopause, including:

- Smoking
- Poor nutrition
- Stress
- Low body weight

Thus, menopause is mainly associated with hormonal changes resulting from ovarian aging or damage to ovarian function.

1.1.3 Treatment of Menopause

The treatment of menopause mainly aims to relieve menopausal symptoms, improve quality of life, and prevent long-term complications such as osteoporosis and cardiovascular diseases. Treatment depends on the severity of symptoms, age of the patient, and overall health condition.

a. Hormone Replacement Therapy (HRT)^[1,3]

Hormone Replacement Therapy is the most effective treatment for menopausal symptoms caused by estrogen deficiency.

Types of HRT

- Estrogen therapy
- Combined estrogen and progesterone therapy

Routes of Administration



- Oral tablets/capsules
- Transdermal patches
- Vaginal creams and rings
- Injectable preparations

Adverse Effects

- Nausea
- Breast tenderness
- Headache
- Risk of thromboembolism
- Increased risk of certain cancers with prolonged use

b. Non-Hormonal Therapy^[8,9,10]

Non-hormonal drugs are used in women who cannot receive hormone therapy.

Drugs Used

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Selective Norepinephrine Reuptake Inhibitors (SNRIs)
- Gabapentin
- Clonidine

These drugs help reduce vasomotor symptoms such as hot flashes.

c. Lifestyle Modifications

Lifestyle changes play an important role in menopause management.

Recommended Measures

- Regular physical exercise
- Healthy balanced diet
- Adequate calcium and vitamin D intake
- Smoking cessation
- Reduction of alcohol and caffeine intake
- Stress management and yoga

d. Alternative and Supportive Therapy

Some women use supportive therapies for symptom relief:

- Phytoestrogens
- Herbal supplements
- Cognitive behavioural therapy
- Relaxation techniques

Thus, appropriate treatment and lifestyle management can effectively reduce menopausal symptoms and improve overall health in postmenopausal women.

1.2 Oral Drug Delivery System

Oral drug delivery system is the most commonly used method for administration of drugs through the oral route to achieve systemic or local therapeutic effects. In this system, the drug is administered by mouth and absorbed through the gastrointestinal tract. Oral dosage forms include tablets, capsules, syrups, suspensions, powders, and solutions. The oral route is widely preferred because it is convenient, non-invasive, economical, and provides better patient compliance compared to other routes of administration.

1.2.1 Capsules

Capsules are solid unit dosage forms in which the drug substance is enclosed within a hard or soft soluble shell made mainly of gelatin or other suitable polymers. Capsules are one of the most widely used oral drug delivery systems because they are easy to swallow, provide accurate dosing, and improve patient compliance. The capsule shell dissolves in the gastrointestinal fluids after administration, releasing the medicament for absorption. Capsules can contain powders, granules, pellets, semi-solids, or liquid



formulations depending on the type of capsule used. **1.2.2 Tablet vs Capsule**

Table no 1: Tablet vs Capsule

Parameter	Tablets	Capsules
Definition	Solid dosage form prepared by compression of powders or granules	Drug enclosed within a hard or soft shell
Structure	Compressed solid unit	Gelatin or polymer shell containing drug
Taste Masking	Less effective	Better taste masking
Swallowing	Sometimes difficult	Easier to swallow
Manufacturing Cost	Economical	More expensive
Drug Release	Slower in some formulations	Faster drug release
Stability	More stable	Sensitive to humidity
Flexibility of Formulation	Limited for liquids	Suitable for powders and liquids
Patient Compliance	Moderate	Better patient compliance
Appearance	Less attractive	Elegant appearance

2. DRUG PROFILE

i. BUTTERFLY PEA^[11-16]



Fig 2.1: Blue pea flower

Synonym: Aparajita, Blue pea, Darwin pea, Asian pigeonwings

Family: Fabaceae (subfamily Faboideae).

Biological source: The biological source of the butterfly pea flower is *Clitoria ternatea* L., a perennial herbaceous plant.

Chemical constituents:

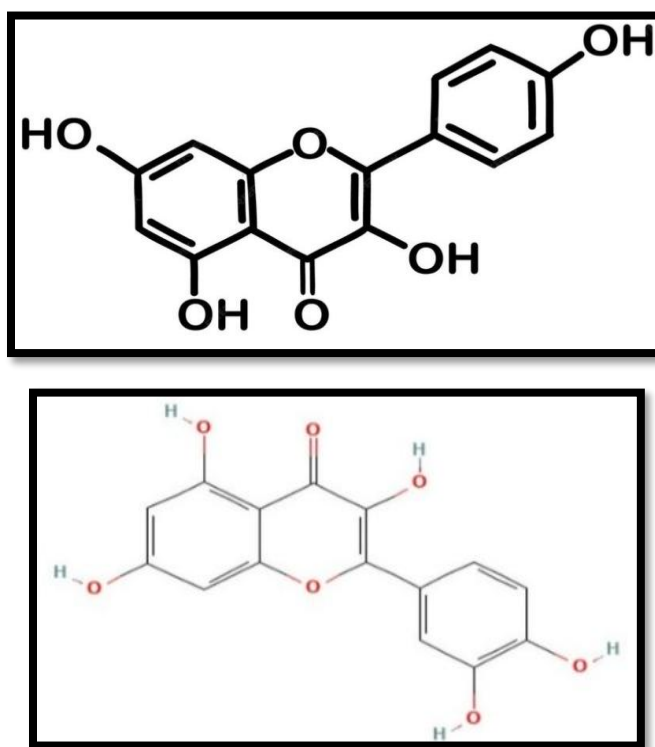


Fig 2.2: Chemical constituents of blue pea

Polyphenolic compounds like kaempferol, anthocyanins, phenolic acid, myricetin, and quercetin are abundant in it. Butterfly pea flowers also include lipophilic components, such as fatty acids like palmitic acid, linolic acid, and arachidic acid; phytosterols like campesterol, sitostanol, and stigmasterol.

Solubility: Highly soluble in water, soluble in polar solvents & insoluble in non-polar solvents.

Pharmacological Profile: Blue pea's antioxidant, neuroprotective, anti-inflammatory, and modest adaptogenic qualities may be beneficial during menopause. Its anthocyanins, flavonoids, and phenolic substances may aid with cognitive decline, anxiety, mood swings, fatigue, oxidative stress, and skin ageing. Its bioactive ingredients have low oral bioavailability due to gastrointestinal instability and significant first-pass metabolism, with metabolites being removed thru urine and bile. The plant predominantly

functions thru non-hormonal mechanisms, such as free radical scavenging, cholinergic activity modulation, and potential stress response regulation, with no significant oestrogen receptor agonistic activity. It is generally well tolerated, but stomach problems, sleepiness, and moderate allergic responses may occur. It is normally avoided during pregnancy and lactation, and it should be used with caution when combined with CNS depressants or antihypertensive medications due to potential synergistic effects.

ii. CHASTEBERRY^[17-22]

Synonyms: Monk's pepper

Biological source: The biological source of Vitex consists of the dried ripe fruits, and occasionally the leaves and flowering tops, of the plant *Vitex agnus-castus*.



Family: Lamiaceae (formerly classified under Verbenaceae).



Fig 2.3: Chasteberry plant & chasteberry seeds

Chemical constituents:

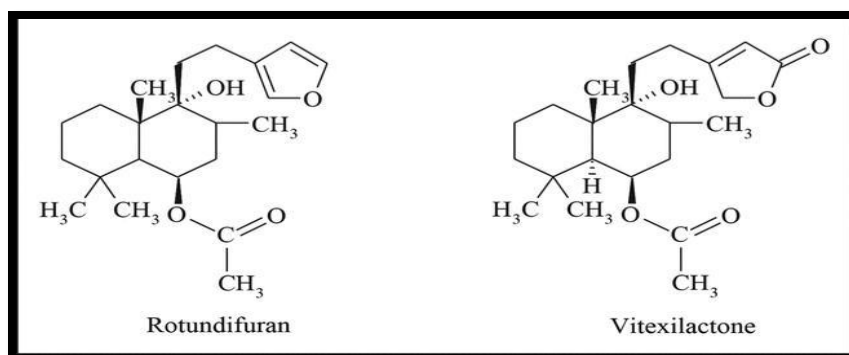


Fig 2.4: Chemical constituents of Vitex agnus-castus

Vitex agnus-castus has a wide variety of pharmacologically significant chemical constituents. Its dopaminergic activity is mainly caused by diterpenoids, which include rotundifuran and vitexilactone, among other major bioactive compounds. The plant also contains iridoid glycosides like aucubin and agnuside, flavonoids like casticin, kaempferol, and quercetagenin, and essential oils.

Solubility: Soluble in polar solvents, insoluble in non-polar & inert solvents

Pharmacological Profile: According to its endocrine-modulating and neuroendocrine properties, Vitex agnus-castus is used as a supportive herbal therapy for menopausal symptoms like mood swings, irritability, hot flashes, sleep disorders, and breast discomfort. Its diterpenoids, flavonoids, and iridoid glycosides mostly work by stimulating dopaminergic D₂ receptors, which lowers prolactin release and aids in controlling the balance of FSH, LH, and reproductive hormones. Its components undergo hepatic metabolism, conjugation, and excretion primarily thru urine and bile following oral dosing;

nevertheless, comprehensive human pharmacokinetic data are scarce. Although chasteberry is usually well accepted, it can cause irregular menstruation, headaches, dizziness, or skin problems. It should be taken with caution in hormone-sensitive disorders, with dopamine-modulating medications or hormone replacement treatment, and during pregnancy and breastfeeding.

3. MATERIAL & METHODS

MATERIALS:

The active compounds in the mixture were ashwagandha, bamboo silica, chasteberry extract,

and blue pea extract, which offered antioxidant, hormonal balance, adaptogenic, and bone-supporting qualities, respectively. Magnesium stearate, ethyl cellulose, microcrystalline cellulose, talc, and HPMC were utilised as lubricant, diluent, glidant, and binder/film forming, respectively. The extracts of blue peas and chasteberries were made in a lab, while the other ingredients were procured from SSJCOP Store and internet retailers.

METHODS:

EXTRACTION METHOD^[17,25,29]

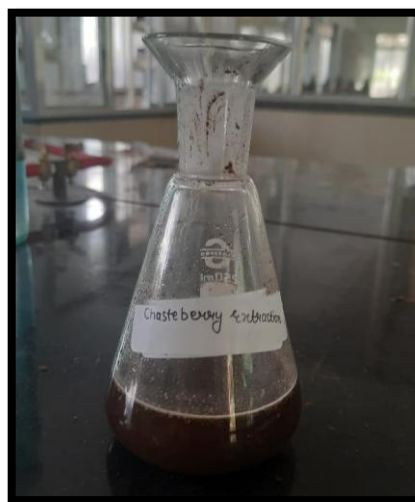
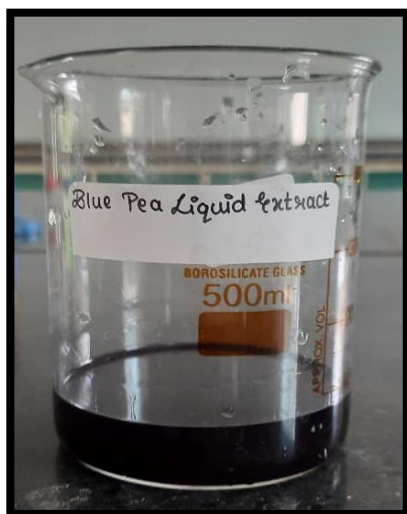


Fig 3.1: Blue pea extract Fig 3.2: Chasteberry extract

Extraction method of Blue pea & Chasteberry

Dried powdered blue pea flowers and chasteberry seeds were taken

↓
Extracted with Ethanol: Water (70:30, v/v) individually

↓
Macerated for 24–72 h with intermittent shaking
↓

Filtration through muslin cloth & Whatmann filter paper

↓
Concentration of filtrate using a water bath
↓
Obtained concentrated extract

↓
Storage in an airtight container



**FORMULATION
METHOD**^[25,28,30]

Accurately weighed quantities of herbal extracts and excipients were mixed uniformly. Binder solution was added gradually with continuous mixing to obtain a coherent damp mass. The wet mass was passed through sieve no.12 to prepare wet granules. The prepared granules were dried in

DEVELOPMENT

a tray dryer or hot air oven at controlled temperature until optimum moisture content was achieved. Dried granules were re-sieved to obtain uniform granule size. Finally, lubricants and glidants were added, mixed properly, and the prepared polyherbal granules were then filled into hard gelatin capsules manually. Capsules stored in airtight container.

Table no 3: Formulation table for composition of polyherbal granules

Sr.no.	Ingredients	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)
1.	Blue pea	30.56	30.56	30.56	30.56	30.56	30.56
2.	Chasteberry	22.22	22.22	22.22	22.22	22.22	22.22
3.	Ashwagandha	19.44	19.44	19.44	19.44	19.44	19.44
4.	Bamboo silica	8.33	8.33	8.33	8.33	8.33	8.33
5.	EC	1.39	1.39	5.56	2.78	1.39	1.39
6.	HPMC	2.78	6.94	2.78	4.17	2.78	2.78
7.	MCC	8.33	8.33	8.33	9.72	9.72	9.72
8.	Talc	1.39	1.39	1.39	1.39	4.17	1.39
9.	Magnesium stearate	1.39	1.39	1.39	1.39	1.39	4.17
	Total weight (in mg)	360 mg	360mg	360mg	360mg	360mg	360mg

4. RESULT & DISCUSSION**Table no 4.1: Organoleptic evaluation of blue pea extract & chasteberry extract**

Parameter	Result (blue pea)	Result (chasteberry)
Colour	Deep blue	Brownish black
Odour	Characteristic aromatic odour	Characteristic aromatic odour
Taste	Slightly bitter	Bitter and slightly pungent
Appearance	Fine dry powder	Fine dry powder
Texture	Smooth and free flowing	Smooth and free flowing





Fig 4.1: Phytochemical evaluation of blue pea extract

Table no 4.2: Phytochemical evaluation of blue pea extract^[11-22]

Test	Observation	Result
Alkaloids	Cream / orange precipitate observed	Present
Flavonoids	Pink / yellow coloration observed	Present
Phenol & Tannins	Blue-black coloration observed	Present
Saponins	Persistent stable foam formation	Present
Glycosides	Brown ring formation at interface	Absent
Terepenoids	Reddish-brown coloration at interface	Present

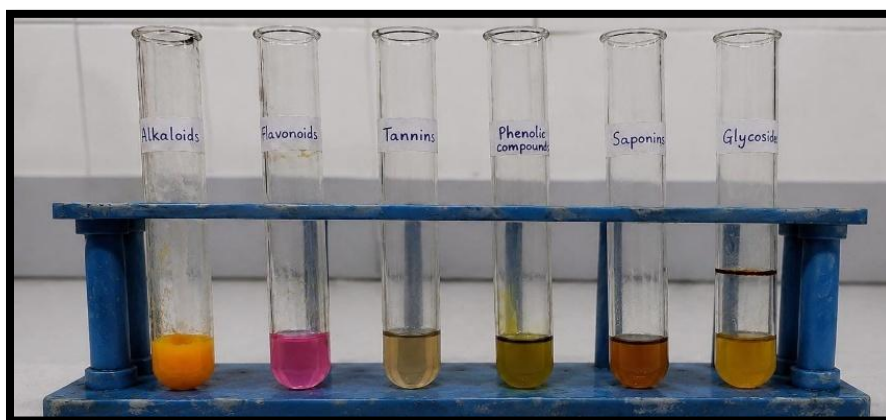


Fig 4.2: Phytochemical evaluation of chasteberry extract

Table no 4.3: Phytochemical evaluation of chasteberry extract^[11-22]

Test	Observation	Result
Alkaloids	Orange precipitate	Present
Flavonoids	Pink colouration produced	Present
Tannins	No greenish black colour observed	Absent
Phenolic compounds	White precipitate	Present
Saponins	No stable foam formation	Absent
Glycosides	Brown Ring formation	Present

Table no 4.4: Evaluation of Flow properties of granules^[26,27,30]

Batch	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
F1	0.45	0.52	13.46 %	1.15	28
F2	0.43	0.50	14.00 %	1.16	30
F3	0.46	0.54	14.81 %	1.17	29
F4	0.48	0.54	11.11 %	1.12	26
F5	0.50	0.56	10.71 %	1.12	25
F6	0.47	0.55	14.54 %	1.17	31



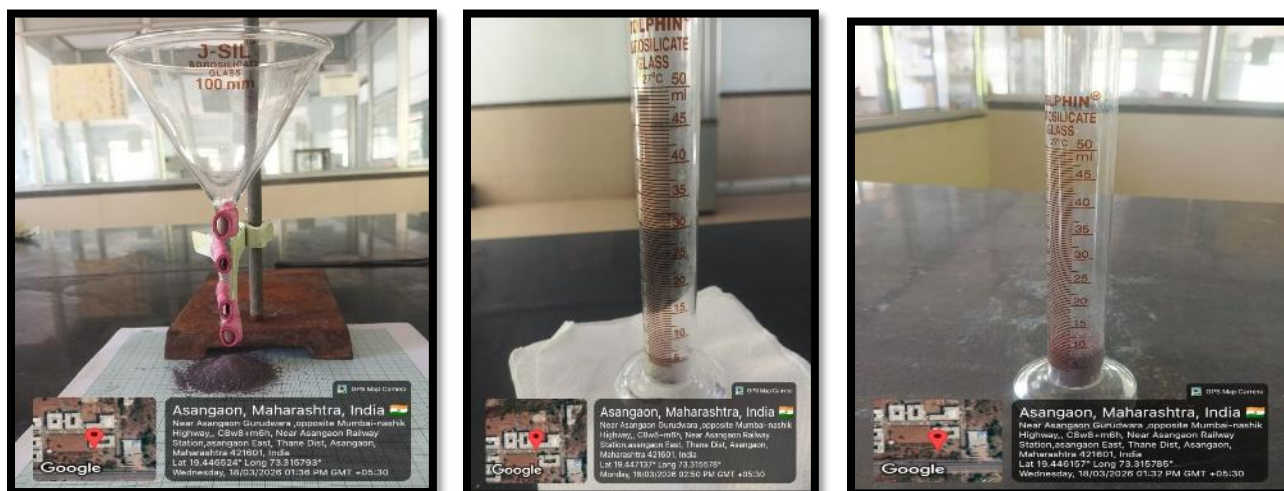


Fig 4.3: Flow properties Evaluation

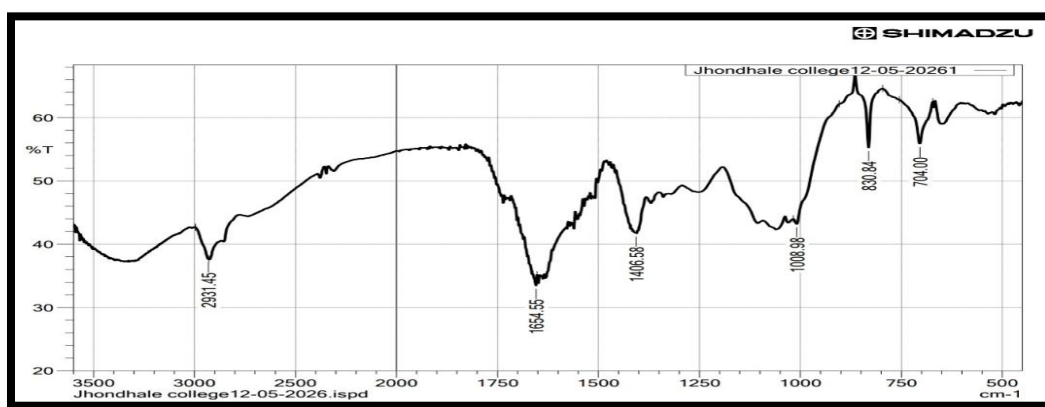


Fig 4.4: FTIR peak of Blue pea and Chasteberry

Table no 4.5: FTIR peak interpretation of drug sample^[25,30]

Peak cm^{-1}	Chemical group	Chemical constituents
2931.45 cm^{-1}	C-H	Terpenoids, iridoids and other aliphatic compounds
1654.55 cm^{-1}	C=O	Flavonoids, anthocyanins and phenolic compounds
1008.98 cm^{-1}	C-O	Flavonoid glycosides and iridoid glycosides
830.84 cm^{-1}	=C-H	Aromatic phytoconstituents

Formulation of granules

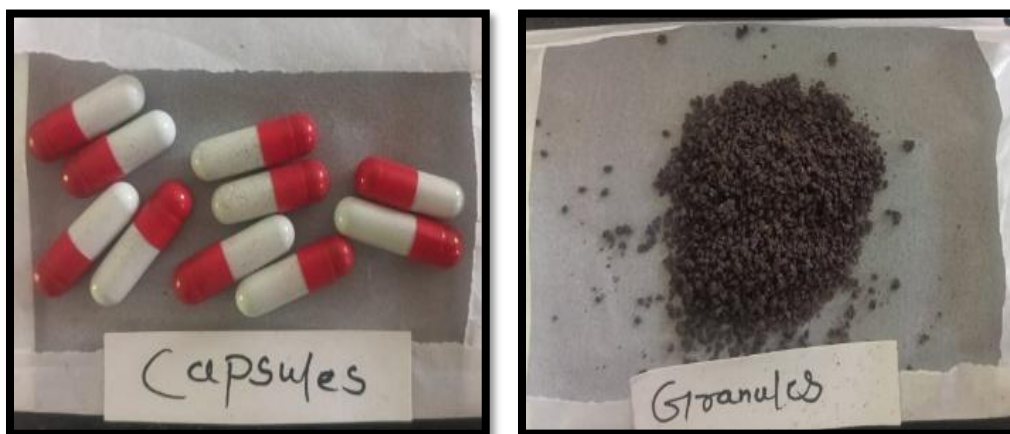


Fig 4.5: Granules & Capsules

❖ Appearance Evaluation

Table no 4.6 : Appearance Evaluation of granules

Parameter	Observation
Colour	Uniform bluish black colour
Odour	Characteristic herbal odour
Surface appearance	Smooth & elegant
Leakage	Absent
Physical defects	No cracks or deformation observed

❖ Solubility test

Table no 4.7: Solubility Study of granules in different medium

Medium	Observation
Water	Partially soluble
Hydrochloric acid	Freely soluble
Sodium hydroxide	Moderately soluble
Overall result	Satisfactory solubility observed

❖ **Weight Variation test****Table no 4.8: Weight Variation test**

Formulation	Average weight (mg)	% Deviation	Result
F1	359	±2.1	Pass
F2	361	±1.8	Pass
F3	364	±6.5	Exceed the limit
F4	362	±1.6	Pass
F5	365	±7.44	Pass
F6	359	±2.4	Exceed the limit

❖ **Content uniformity Test****Table no 4.9: Content uniformity Test**

Formulation	Drug content (%)	Result
F1	96.2 %	Uniform
F2	98.4 %	Uniform
F3	99-100 %	Uniform
F4	98.0 %	Uniform
F5	98.9-99.0 %	Uniform
F6	96.5 %	Uniform

❖ **Moisture content Test****Table no 4.10: Moisture content test**

Formulation	Moisture content (%w/w)	Result
F1	4.5	Acceptable
F2	4.2	Acceptable
F3	4.8	Acceptable
F4	4.4	Acceptable



F5	4.9	Acceptable
F6	5.0	Acceptable

❖ **Dissolution Test****Table no 4.11: Dissolution test^[28,30]**

Formulation	Absorbance at 30 min	% Drug release	Observation
F1	0.712	82.4 %	Moderate drug release observed
F2	0.756	86.8 %	Improved dissolution profile
F3	0.804	91.2 %	Uniform drug release obtained
F4	0.836	94.5 %	Rapid dissolution observed
F5	0.861	97.1 %	Nearly complete drug release
F6	0.875	98.4 %	Maximum drug release achieved

❖ **Disintegration Test****Table no 4.12: Disintegration Test^[28,30]**

Formulation	Avg. disintegration time (min)	Observation
F1	10.24	Complete disintegration observed
F2	09.48	Uniform disintegration observed
F3	08.36	Rapid & complete disintegration



F4	08.12	Satisfactory disintegration behaviour
F5	07.54	Faster disintegration observed
F6	07.32	Complete & uniform disintegration

❖ Antimicrobial test

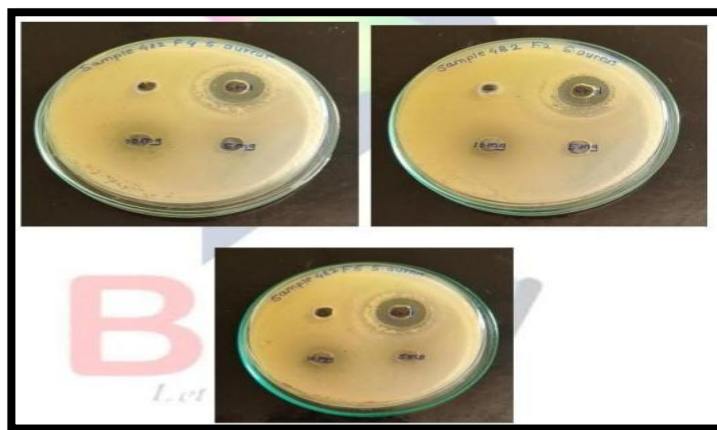


Fig 4.6: Antimicrobial test

Table no 4.13: Antimicrobial test^[18,19]

Sr.no	Sample	Concentration	Zone of Inhibition
1	Control	-	-
2	Standard Streptomycin	1 mg/ml	35
3	Sample -BP CB- F2	5mg/mL	02
		10mg/mL	06
4	Sample -BP CB- F4	5 mg/mL	02
		10mg/mL	10
5	Sample -BP CB- F5	5 mg/mL	03
		10mg/mL	14

❖ Stability studies

Table no 4.14: Stability studies^[28,30]

PARAMETER	Formulation code	Initial	After 15 days	After 30 days
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Physical appearance	F1 to F6	Good physical appearance	Good physical appearance	Good physical appearance
Colour stability	F1 to F6	Bluish black colour	Stable	Stable
Odour	F1 to F6	Characteristic odour	No change	No change
Moisture content	F1 to F6	Within limits	Within limits	Within limits

5. SUMMARY & CONCLUSION

❖ Summary

The present research work was focused on the development and evaluation of herbal capsules containing standardized extracts of *Clitoria ternatea* and *Vitex agnus-castus* for the management of menopausal symptoms. The formulation was designed to provide a natural and safe alternative to conventional hormone therapy with improved patient compliance. The selected herbal drugs were extracted and subjected to phytochemical, physicochemical, and solubility studies. The results confirmed the presence of bioactive constituents such as flavonoids, phenolics, anthocyanins, and iridoid glycosides which are responsible for antioxidant, neuroprotective, and hormonal balancing activities.

The formulated capsules were evaluated for physical parameters including appearance, weight variation, flow properties, and capsule integrity. The results showed uniform filling, good flow characteristics, and absence of leakage or physical defects. The in vitro drug release study showed a satisfactory and controlled release of herbal constituents with maximum release observed within 45 minutes. The formulation also exhibited acceptable disintegration time and uniform content distribution, indicating good performance characteristics. Stability evaluation conducted

under laboratory conditions showed no significant changes in physical appearance, drug content, or dissolution behavior, indicating that the formulation is stable under the tested conditions.

❖ CONCLUSION

The present study successfully developed and evaluated polyherbal granules filled in hard gelatin capsules containing *Clitoria ternatea* and *Vitex agnus-castus* for the management of menopausal symptoms. The prepared formulations were evaluated for various preformulation and postformulation parameters including flow properties, appearance, solubility, weight variation, content uniformity, moisture content, dissolution, disintegration, antimicrobial activity, and stability studies. [45,46,47,48] The granules exhibited satisfactory flow characteristics with acceptable bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose, indicating good flowability and suitability for capsule filling. FTIR studies confirmed the compatibility of herbal ingredients and excipients without significant interaction.

All formulations showed acceptable physical appearance, satisfactory solubility, good capsule integrity, and uniform drug content. The formulations also demonstrated acceptable moisture content, effective dissolution behaviour, rapid disintegration, and satisfactory stability during the study period. [60]



Among all the formulations, **Batch F3 and Batch F5** were identified as the optimized formulations based on their superior evaluation parameters.

- **F3** showed good content uniformity, satisfactory dissolution, rapid disintegration, and uniform drug release characteristics.
- **F5** exhibited excellent dissolution profile, faster disintegration time, good antimicrobial activity, and stable formulation behaviour.

Therefore, the study concludes that F3 and F5 are the best formulations, with F5 considered the best overall batch due to its enhanced drug release, faster disintegration, and better overall performance for effective management of menopausal symptoms.

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