# A Novel Solvent-Free Polyherbal Triple-Layer Capsule of Euphorbia Hirta, Gymnema Sylvestre And Trigonella Foenum-Graecum For Controlled Diabetes Therapy And Wound Healing

**R.Abishek[1], Mrs.K.Malarvizhi[2]**
[1]Dept of pharmaceutics
[2]Associate professor, Dept of pharmaceutics

***Abstract-*** *The current study addresses the innovative design and development of a new, eco-friendly triple-layer herbal capsule aimed at managing diabetes mellitus and its chronic complications, with a specific emphasis on impaired wound healing. This novel capsule incorporates the three herbal substances Gymnema sylvestre, Euphorbia hirta, and Trigonella foenum-graecum, and each of them has been embedded in a particular layer of the capsule to allow sequential release of the ingredients, thus addressing several stages and sites of diabetes-related pathology. The herbal capsule is formulated using direct compression, dry granulation, and dry powder coating, which ensures no residual solvents are present, thus contributing to pharmaceutical sustainability.*

*Each layer of the capsule is designed to release the actives at a specific target site for a function-specific action.*

***Layer 1*** *(Outer Layer): The outermost layer is Euphorbia hirta, which is rich in flavonoids that have antioxidant properties and can heal wounds. It is designed for immediate gastric disintegration to dampen oxidative stress and microbial load as early as possible.*

***Layer 2*** *(Middle Layer): The middle layer is Gymnema Sylvestre, which has gymnema acids that aim for controlled gastric release in the upper intestine to achieve inhibition of glucose absorption and stimulation of insulin secretion.*

***Layer 3*** *(Core Layer): The core layer is Trigonella foenum-graecum (fenugreek), which is rich in saponins and galactomannans. It is designed for sustained release in the distal gut to achieve long-term control of anti-inflammatory and anti-glycemic action.*

*Phytoconstituents were obtained using green techniques and characterized through preliminary phytochemical screening and UV vis spectroscopy. The evaluation plan includes testing Excipient blending and micro particle sizing, physicochemical attributes, and disintegration and dissolution testing in simulated gastrointestinal fluids, bioactive marker spectrophotometry, and quantitation by marker ratio method. Assessing the antioxidant capacity by DPPH method and bioactive relevance through glucose uptake analysis.*

*This system for delivery tackles the various aspects of diabetes by improving formulation, phytochemical stability, adherence, and phytochemical stability of the medication. The solvent-free, site-specific method used in this case can be applied to various other cases, which makes it ideal for patenting and progression through regulatory requirements. In this case, the next steps will be the in vitro release assays, diastolic and systolic function preclinical studies, and thorough stability studies to facilitate a faster time to market*

***Keywords***- Triple-layer capsule; Herbal formulation; Diabetes mellitus; Solvent-free techniques; Euphorbia hirta; Gymnema sylvestre; Trigonella foenum-graecum; Wound healing; Green pharmacy; Phase-wise drug release.

## I. INTRODUCTION

Diabetes mellitus (DM) is a sophisticated and chronic endocrine disorder characterized by sustained elevation of blood glucose levels due to insufficient insulin secretion, reduced insulin sensitivity, or both. It consists of several metabolic syndromes that affect the metabolism of carbohydrates, lipids, and proteins, impacting multiple organs and systems. The increasing incidence of diabetes Worldwide is a significant issue for public health. The International Diabetes Federation (IDF) estimates that the diabetes population will surpass 783 million people by 2045.[1].The geographic distribution of diabetes prevalence is shown in figure 1. Countries like India bear a significant health burden

due to rapid lifestyle changes, increased urbanization, and genetic predisposition.

One of the most concerning aspects is its chronic complications, which concern the cardiovasculatory system, neuropathy, nephropathy, retinopathy, and even diabetes associated foot ulcers. Of these, the slow healing of wounds is particularly underappreciated, even as it contributes most to hospitalizations and amputations among diabetes patients. A multitude of factors make diabetes wounds difficult to repair, such as inadequate blood circulation, insufficient formation of new blood vessels, heightened oxidative stress, infection, and prolonged inflammation. Aside from these factors, achieving effective glucose levels is essential, as well as addressing tissue restoration, microbial resistance, and oxidative stress damage.[2]

Synthetic antidiabetic drugs are available; however, they come with adverse effects like gastrointestinal problems, hypoglycemia, and organ damage over extended periods of use [3]. This has prompted the use of some herbal drugs, as they are less likely to cause adverse reactions and work on multiple therapeutic targets. Certain medicinal plants like Gymnema sylvestre, Euphorbia hirta, and Trigonella foenum-graecum have shown potent antidiabetic, antioxidant, anti-inflammatory, and wound healing activities in various experimental studies [4–7]. However, conventional dosage forms are faced with poor bioavailability, the absence of controlled release, and the lack of stability of the phytoconstituents.

This study aims to introduce an innovative triple-layer herbal capsule designed for phase-specific and site-specific drug delivery to overcome these limitations. Each layer of the capsule has a targeted herbal component with a specific herbal action. The outer layer is Euphorbia hirta, which is released immediately in the stomach to counter oxidative stress and to initiate wound modulation; the middle layer is Gymnema sylvestre, which is released in the upper intestine for anti-glycemic action by inhibition of glucose absorption and stimulation of insulin secretion; and the core is Trigonella foenum-graecum with controlled release in the distal gut to provide sustained release for long-term anti-glycemic and anti-inflammatory action.

Notably, this approach still uses environmentally safe methods of production like direct compression, dry granulation, and dry powder coating, meaning there is no residual toxicity. The project also includes assessment of the antioxidant activity by DPPH assay, in vitro glucose uptake assays, and phytochemical profiling coupled with UV-visible spectral analyses for comprehensive evaluation of the therapeutic properties of the formulated capsule. This method improves the effectiveness and stability of the herbal constituents while improving patient adherence and compliance through minimized dosing frequency. This is substantial progress toward the integration of green technologies into the pharmaceutical industry, adhering to the principles of eco-friendly drug development. Further work will concentrate on establishing the in vitro and in vivo pharmacokinetic and pharmacodynamic profiles of the formulated system to make it ready for clinical and commercial use.

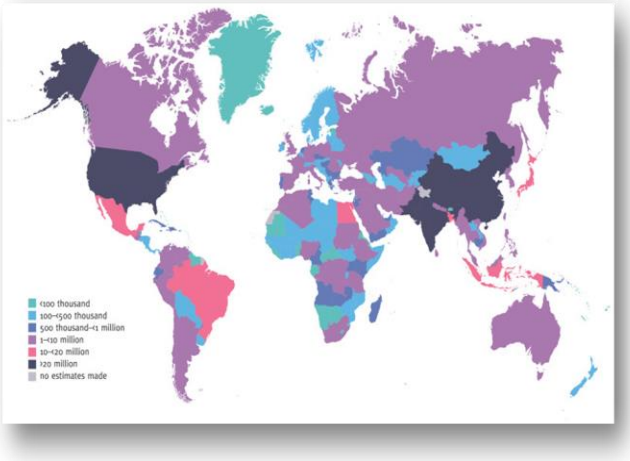


Figure 1. Global distribution of diabetes prevalence in adults aged 20–79 years (2021). Source: IDF Diabetes Atlas, 10th edition [1].

## II. LITERATURE REVIEW

### 1. Diabetes and Its Complications

Diabetes mellitus poses a serious and growing challenge to public health worldwide. The number of people living with diabetes is projected to increase to 783 million individuals by 2045 (IDF, 2023). This condition's chronic hyperglycemia complications of cardiovascular diseases, nephropathy, neuropathy, and, perhaps most importantly, oxidative stress and inflammatory response-induced wound healing complications (Forbes & Cooper, 2013).The polyol pathway is one of the major mechanisms by which persistent hyperglycemia induces oxidative stress, leading to vascular impairment and diabetic complications (Figure 2).Diabetes is a challenge, requiring coordinated and simultaneous hypoglycemic, anti-inflammatory, and regenerative therapies.

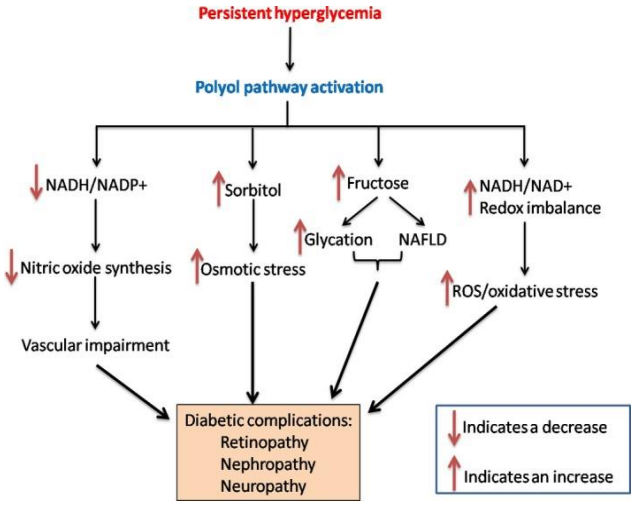


Figure 2. Polyol pathway activation under persistent hyperglycemia leading to oxidative stress and diabetic complications. Adapted from Yan LJ. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. Anim Models Exp Med. 2018;1(1):7–13.[9]

## 2. Challenges in conventional anti diabetic therapies

Concerns in Antidiabetic Treatment Both traditional and newer therapies with insulin, metformin, and sulfonylureas, as well as DPP-4 inhibitors, might control blood glucose levels, but worsen the condition with hypoglycemic states, gastrointestinal inflammation, and even resistance with chronic use (Bailey & Day, 2004)., as well as neglecting the wound healing component of diabetes, has led to a surge of interest to treat this problem with low toxicity herbal alternatives that offer a myriad of activities high effectiveness and low toxicity.

## 3.Role of herbal medicine in diabetes and wound healing

Antidiabetic herbal formulation enriched with antioxidants, polyphenols, flavonoids, and saponins helps regulate blood glucose by aiding in its promotion to blood sugar control, as well as collagen and antimicrobial activities.(Modak et al..,2007)

## 3. Therapeutic Uses of Selected Herbs

Euphorbia Hirta: Used traditionally for respiratory and gastrointestinal ailments, Euphorbia hirta has an extensive array of bioactive compounds, such as flavonoids, terpenoids, and tannins. Its herbal medicinal properties are backed by science. Recently, its potent antioxidant and antimicrobial activities, important for diabetic wound healing, have garnered attention (Sasidharan et al., 2011). In addition, Euphorbia hirta's anti-inflammatory activity can help in tissue regeneration of cutaneous wounds.

Figure 3: euphorbia hirta commonly known as asthma weed, traditionally used for its antidiabetic and wound healing potential. Adapted from Wikimedia commons

Gymnema sylvestre: Its popular name is “sugar destroyer” as it is known to curb diabetes. Gymnema sylvestre has gymnemic acids, which reduce the absorption of glucose in the intestine and stimulate regeneration of the pancreatic beta-cells (Shanmugasundaram et al., 1990). Its effectiveness in decreasing HbA1c and increasing insulin sensitivity has been confirmed in clinical studies.

Figure 4: Gymnema sylvestre .Adapted from Wikimedia commons

Trigonella foenum-graecum (Fenugreek): Fenugreek is famous for its seeds, which are rich in various compounds such as galactomannans, saponins and 4-hydroxyisoleucine, which have hypoglycemic, hypolipidemic and anti-inflammatory activities. Furthermore, its mucilaginous property enables it to provide regenerative scaffolds for wound repair in diabetes. Has been reported (Basch et al., 2003).

Figure 5: Trigonella foenum- graecum seeds. Adapted from Wikimedia commons

**5. Addressing Phase-Specific Delivery Needs in Multi-Component Herbal Therapeutics**

The multi-component herbal systems face challenges like low bioavailability, degradation within the GI tract, and the release profile being erratic. A phase-specific, layered capsule design solves these problems by releasing each herb at the optimal site of action.

Gastric release: (E. hirta) → antioxidant action.

Intestinal release (G. sylvestre) → glucose modulation.

Distal release (T. foenum-graecum) → prolonged hypoglycemia and regeneration.

**6. Eco-Friendly Innovation: Sustainability Through Solvent-Free Formulation**

Herbal extractions and formulations are often done with organic solvents that may leave toxic residues. Eco-safety and scalability are enhanced with direct compression, dry granulation, and powder layering (Rasenack & Müller, 2004)

**7. Concept Justification**

Integrated systems that combine multiple herbs into a single controlled-release formulation are still a rare occurrence in herbal diabetes and wound care research. Additionally, the lack of sustainability in herbal drug processing is a significant gap in the field. This is where the current concept of a triple-layer, solvent-free capsule aims to fill, bridging a gap where phytotherapy meets modern systems. (Sasidharan et al., 2011; Shanmugasundaram et al., 1990; Basch et al., 2003; Rasenack & Müller, 2004).

## III. MATERIALS AND METHODS

**Materials**

The active herbal extracts selected for this study are Euphorbia hirta (aerial parts), Gymnema sylvestre (leaves), and Trigonella foenum-graecum (seeds). These plants were selected based on their pharmacological activities associated with diabetes management, inflammation, and wound healing. All raw plant materials were assumed to be authenticated by a qualified botanist, and voucher specimens were kept for reference.

Excipients of this proposed formulation include:

**Microcrystalline cellulose (MCC):** Used as a direct compression filler because of the high compressibility and cohesiveness of the bonds, which were critical for non-solvent methods [8].

**Magnesium stearate**: lubricant.

**Hydroxypropyl methylcellulose (HPMC):** used for dry powder coating.

**Lactose monohydrate**: a diluent (with optional use).
All excipients were of pharmaceutical grade and were compatible with non-solvent methods.

**Formulation Design**:

The three-layer capsule is intended for phase-specific release, where each layer serves a different therapeutic purpose.

1. **Outer Layer (Layer 1):** Euphorbia hirta. Fabricated using dry granulation to maintain low moisture content and avoid organic solvents.

**Target**: gastric release for wound healing and antioxidant action. A layer formed by compression blending with MCC and magnesium stearate.

2. **Intermediate Layer (Layer 2):**

**Gymnemasylvestre**.
Formulated by direct compression to maintain compactness without the use of solvents.

**Target**: upper intestine (duodenum) for glycemic control.
Used with HPMC for the desired controlled release.

3. **Core Layer (Layer 3):**

Trigonella foenum-graecum prepared as a delayed-release matrix core.

**Target**: distal gut for sustained glucose control and anti-inflammatory activity. Dry granulated and encapsulated with an HPMC coating for delayed release.

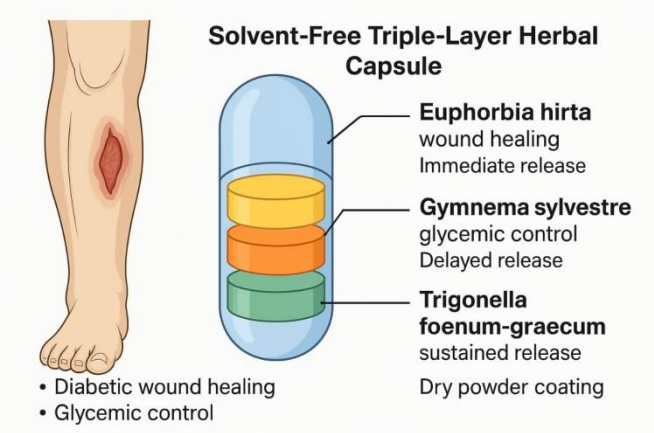


**Figure 6: Solvent free triple layer capsule**

**EncapsulationProcedure**.

Each layer was manufactured separately and assembled later: Dry granulated powders of each herb were mini tablet layered compressed in a multilayer tablet compression machine, or were manually capsule layered in a conceptual stage. Assembled in a gelatin capsule apparatus: Starts with T. foenum-graecum core, followed by G. sylvestre and capped with E. hirta as the top layer.

No solvents, no binders, no granulating fluids were employed, guaranteeing environmental safety and preservation of phytochemicals.

**Proposed evaluation parameters:**

**1. Preformulation Studies:**

Flow Properties: Angle of repose and Carr's index.
Moisture content analysis: loss on drying.

**2. Post Formulation Evaluation:**

Weight and thickness uniformity assessment.
Layer-wise disintegration and dissolution profiling in simulated GI fluids.
Stability assessment under accelerated conditions.

**3. Planned Pharmacological Screening:**

Antioxidant assessment: DPPH radical scavenging assay.
Glucose uptake estimation using 3T3-L1 or L6 cell lines.
In vitro assessment of wound healing: scratch assay or fibroblast growth test

## IV. RESULTS AND DISCUSSION

While the current research is of a conceptual nature and does not present empirical findings, the expected outcomes have been estimated considering the pharmacological properties of each plant extract and the planned dosage forms.

**1. Antioxidant Activity (DPPH Method)**

Based on the presence of flavonoid constituents, Euphorbia hirta is expected to have a strong DPPH radical scavenging effect, reversing oxidative damage related to diabetes and wound healing complications [5].

**Expected Outcome:** Strong antioxidant activity will be observed in the outer layer with E. hirta, supporting the hypothesis that E. hirta addresses the pathology at an early stage.

**2. Glucose Uptake Assay (3T3-L1 or L6 Cell Lines)**

Gymnema sylvestre is expected to markedly improve glucose utilization in insulin-responsive cell lines through stimulation of insulin secretion, GLUT-4 expression, and intestinal glucose transport inhibition [6].

**Expected Outcome**: The advanced glucose utilization supports the middle layer's antidiabetic activity.

**3. In Vitro Wound Healing (Scratch Assay / Fibroblast Proliferation)**

It is anticipated that the epithelial core layer of Trigonella foenum-graecum will aid in wound healing through its action on fibroblast proliferation, inflammation, and collagen formation. [7].

**ExpectedOutcome**: In scratch assays, wounds are expected to close faster and show increased cellular migration.

**4. Disintegration and Dissolution Studies Capsule multilayer:**

1. Gastro 1: Layer 1 gastric pH (within 15 minutes)
2. Gastro 2: Layer 2 Upper intestine ~2–4 hours
3. Gastro 3: Layer 3 distal gut 6–8 hours.

This release profile is in accord with pharmacokinetic requirements observed: rapid delivery of antioxidant defense, mid-phase intervention of glycemic levels, and prolonged healing of the tissue.

**5. Synergistic Therapeutic Action:**

Multifactorial benefits are achieved for:

Reducing oxidative stress,
Reducing insulin activity and modulating glucose metabolism activity, Enhancing skin healing and tissue formation.
The triple-layer system further enhances multifunctional benefits by improving phytochemical stability and bioavailability.

## V. CONCLUSION

The novel eco-friendly technique for managing diabetes mellitus and its complications, especially concerning wound healing, is a strategically designed triple-layer herbal capsule. The capsule's design enables phase-specific drug delivery required for diabetic patients by incorporating Euphorbia hirta, Gymnema sylvestre, and Trigonella foenum-graecum in separate formulation layers. The triple-layer capsule maintains eco-friendly pharmaceutical principles through solvent-free manufacturing methods, including dry granulation, direct compression, and dry powder coating. In addition, these methods improve the phytoconstituent's stability and safety. Each layer of the capsule has a critical therapeutic role:

layer 1 provides early wound modulation and antioxidant defense, layer 2 supports insulin and glucose-dependent diabetes by potentiation and stimulated glycemic control, and layer 3 provides anti-inflammatory response and prolonged wound healing.

While awaiting experimental verification, this formulation plan is complemented by existing literature as well as trends in green pharmacy, phytotherapeutics, and targeted drug delivery. The multifunctional and modular structural design of this capsule is promising for clinical translation, as well as for securing intellectual property and regulatory approval.

In vitro characterization and bioefficacy assays, as well as stability and pharmacokinetic profiling, will be conducted in further research to establish the proof of concept for this system and advance it towards commercial use.

## REFERENCES

[1] International Diabetes Federation (IDF). IDF Diabetes Atlas, 10th edition. Brussels: IDF; 2023.
[2] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137–188.
[3] Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. Diabetes Care. 2004;27(8):213–221.
[4] Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TPA. Indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr. 2007;40(3):163–173.
[5] Sasidharan S, Chen Y, Saravanan D, Sundram KM, Latha LY. Extraction, isolation and characterization of bioactive compounds from plants' extracts. African J Tradit Complement Altern Med. 2011;8(1):1–10.
[6] Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Ethnopharmacol. 1990;30(3):265–279.
[7] Basch E, Gabardi S, Ulbricht C. Therapeutic applications of fenugreek. Altern Med Rev. 2003;8(1):20–27.
[8] Rasenack N, Müller BW. Drug release from multiparticulate dosage forms: Influence of pellet coating thickness on release profile. Int J Pharm. 2004;271(1–2):59–69.
[9] Yan LJ. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. Animal Models and Experimental Medicine. 2018;1