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Formulation and Evaluation of a Phytosomal Delivery System of Syzygium cumini in Combination with Metformin for Enhanced Antidiabetic Efficacy

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Abstract: Type 2 Diabetes Mellitus (T2DM) remains a profound global health challenge requiring therapeutic strategies that optimize efficacy while minimizing side effects. This study investigates the development, characterization, and *in-vitro* therapeutic evaluation of an advanced phytosomal delivery system co-encapsulating Metformin Hydrochloride and Syzygium cumini (Jamun) seed extract. Phytosomes were prepared using the solvent evaporation method, with the formulation optimized at a 1:3 drug-to-phospholipid ratio (Batch F3). The optimized formulation exhibited an average particle size of 186 ± 5 nm, a Polydispersity Index (PDI) of 0.214, a Zeta Potential of -31.6 ± 0.7 mV, and an outstanding entrapment efficiency of 88.6% ± 1.1%. Structural integrity and compatibility were confirmed via Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC), showing the successful conversion of crystalline drugs into an amorphous state within the phospholipid matrix. Morphological analysis via SEM/TEM revealed uniform spherical nanovesicles. In-vitro dissolution profiles displayed a sustained drug release of 84.5% ± 1.3% at 8 hours, extending up to 95.6% over 12 hours. Furthermore, the phytosomal system exhibited superior synergistic efficacy, showing enhanced DPPH antioxidant radical scavenging (84.2% ± 1.2%), α-amylase inhibition (82.6% ± 1.2%), and α-glucosidase inhibition (86.1% ± 1.1%) compared to pure Metformin and crude extract alone. These results indicate that the developed phytosomal complex significantly enhances the delivery and therapeutic potential of the combined agents, offering a promising alternative for long-term diabetes management.

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metformin Hydrochloride is widely prescribed as the first-line oral hypoglycemic agent for Type 2 Diabetes Mellitus (T2DM). However, its clinical use is often constrained by high dosing frequencies, low lipophilicity, poor membrane permeability, and systemic gastrointestinal side effects such as nausea, abdominal discomfort, and diarrhea.

Concurrently, herbal therapeutics have gained massive traction due to their multi-targeted mechanisms and lower toxicity profiles. *Syzygium cumini* (commonly known as Jamun or black plum) has been traditionally revered for its potent antidiabetic, antioxidant, and anti-inflammatory properties, primarily attributed to bioactive polyphenols, flavonoids, and anthocyanins present in its seeds. However, raw herbal extracts typically suffer from poor absorption, rapid metabolism, and low oral bioavailability due

to their highly hydrophilic nature, which prevents them from effectively crossing lipid-rich biological membranes.

To overcome these formulation bottlenecks, lipid-based nanocarriers—specifically **phytosomes**—have emerged as an innovative breakthrough. Unlike conventional liposomes where the drug is merely entrapped in an aqueous core, phytosomes involve the formation of stoichiometric chemical complexes between phosphatidylcholine and the active phytoconstituents. This structural arrangement creates a highly lipophilic outer layer that significantly enhances cell membrane permeation, physical stability, and bioavailability.

This research outlines the formulation, optimization, physicochemical characterization, and in-vitro performance evaluation of a novel, synergistic phytosomal complex combining *Syzygium cumini* extract and Metformin Hydrochloride to achieve controlled release and enhanced antidiabetic activity.

2. Materials and Methods

2.1 Materials

Metformin Hydrochloride and Soya Phosphatidylcholine (Phospholipon 90G) were acquired. Seeds of *Syzygium cumini* were authenticated, dried, and extracted utilizing an ethanolic solvent extraction process. All other chemicals and solvents used were of analytical grade.

2.2 Preparation of Phytosomal Complex

The phytosomes were prepared using the **solvent evaporation method**.

1. **Ratio Variation:** Different batches (F1 to F5) were formulated by varying the weight ratios of the combined active ingredients (*Syzygium cumini* extract + Metformin HCl) to Soya Phosphatidylcholine.
2. **Reaction:** The active ingredients and Soya Phosphatidylcholine were dissolved in a round-bottom flask containing an organic solvent mixture of dichloromethane and methanol.
3. **Evaporation:** The mixture was stirred continuously at a controlled temperature of 45°C. The solvent was subsequently removed under reduced pressure using a rotary vacuum evaporator to yield a thin, translucent lipid-drug film.
4. **Hydration:** The thin film was hydrated using a phosphate buffer (pH 6.8) to spontaneously form phytosomal vesicles, which were then subjected to probe sonication to achieve a uniform nano-sized distribution.
5. **Optimization:** Batch **F3**, featuring a **1:3 drug-to-phospholipid ratio**, was identified as the optimized formulation based on morphology and encapsulation efficiency.

3. Characterization and Evaluation

3.1 Particle Size, Polydispersity Index (PDI), and Zeta Potential

The mean vesicle size, size distribution (PDI), and surface charge (Zeta Potential) of the optimized phytosomes (Batch F3) were determined using Dynamic Light Scattering (DLS) and electrophoretic light scattering on a Malvern Zetasizer at 25°C.

3.2 Entrapment Efficiency (% EE)

The percentage of Metformin HCl and bioactive markers encapsulated within the phytosomal vesicles was determined by separating the unentrapped drug using high-speed cooling centrifugation at 15,000 rpm for 45 minutes. The supernatant was analyzed using UV-Visible spectroscopy, and the % EE was calculated as follows:

$$\text{EE (\%)} = \left(\frac{\text{Total Drug Added} - \text{Free Unentrapped Drug}}{\text{Total Drug Added}} \right) \times 100$$

3.3 Instrumental Characterization

- **Fourier Transform Infrared (FTIR) Spectroscopy:** FTIR spectra of pure Metformin, raw plant extract, physical mixtures, and the optimized phytosomal complex (F3) were recorded over the range of $4000 \text{ to } 400 \text{ cm}^{-1}$ to assess molecular chemical interactions.
- **Differential Scanning Calorimetry (DSC):** Thermal behavior and crystallinity profiles were recorded under a constant nitrogen purge with a heating rate of 10°C/min.
- **Surface Morphology (SEM & TEM):** Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) were utilized to observe the outer surface texture, shape, and internal core-shell boundary of the vesicles.

3.4 *In-Vitro* Drug Release Study

In-vitro dissolution profiles were evaluated using a USP Type II dissolution apparatus (Paddle method) in 900 mL of phosphate buffer (pH 6.8) maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Samples were withdrawn at predefined time intervals, replaced with fresh medium, and analyzed spectrophotometrically.

3.5 *In-Vitro* Antidiabetic and Antioxidant Efficacy

- **DPPH Radical Scavenging Assay:** Used to determine antioxidant activity. Reaction mixtures containing DPPH solution and varying concentrations of the test formulations were incubated in the dark, and absorbance was measured at 517 nm.
- **α-Amylase and α-Glucosidase Inhibition Assays:** Formulations were incubated with respective enzymes and substrates (starch and p-nitrophenyl-α-D-glucopyranoside) to assess carbohydrate-digesting enzyme restriction capacity.

4. Results and Discussion

4.1 Physicochemical and Morphological Analysis

The solvent evaporation technique yielded high-quality nano-sized phytosomes. The characterization results for the optimized batch **F3** are detailed below:

- **Vesicle Size & Distribution:** The average particle size was recorded at **186 ± 5 nm**. The PDI of **0.214** indicated a highly uniform and monodisperse system.
- **Zeta Potential:** The surface charge was measured at **-31.6 ± 0.7 mV**. A high negative charge prevents vesicle aggregation due to strong electrostatic repulsion forces, maintaining excellent physical stability.
- **Entrapment Efficiency:** Batch F3 recorded a high entrapment efficiency of **88.6% ± 1.1%**. This high capacity is attributed to the strong affinity of the drug molecules to form non-covalent hydrogen and hydrophobic bonds with the polar head-group of Soya Phosphatidylcholine.
- **Morphology:** Electron micrographs (SEM/TEM) confirmed distinct, spherical vesicles with a well-defined lipid bilayer. The actual individual vesicle sizes ranged between **60 and 120 nm**, validating nanovesicular formation.

4.2 Structural and Thermal Behavior

- **FTIR Spectroscopy:** The FTIR spectrum of Metformin HCl displayed characteristic peaks corresponding to N–H stretching and C=N stretching. The *Syzygium cumini* extract spectrum showed broad peaks indicative of polyphenolic and hydroxyl groups. The F3 phytosome spectrum maintained these signature peaks without any major shifts or appearance of new chemical bands, confirming chemical compatibility and structural preservation of both agents within the complex.
- **DSC Thermograms:** The thermogram of pure crystalline Metformin HCl exhibited a sharp, intense endothermic melting peak. In the DSC thermogram of the phytosomal complex, this

crystalline peak was significantly broadened and suppressed, indicating that the drug was molecularly dispersed in an amorphous state within the phospholipid matrix.

4.3 *In-Vitro* Release and Synergistic Performance Profiles

The *in-vitro* drug release study showcased a sustained biphasic release profile. A controlled, initial burst release was observed, followed by a steady, sustained release reaching **84.5% ± 1.3% at 8 hours**, and extending up to **95.6% at 12 hours**. This extended profile is essential for maintaining steady therapeutic plasma concentrations.

The comparative in-vitro bio-efficacy results are summarized in the table below:

Formulation / Sample	***In-Vitro* Drug Release (at 8 Hours)**	**DPPH Radical Scavenging (%)**	**α-Amylase Inhibition (%)**	**α-Glucosidase Inhibition (%)**
Pure Metformin HCl	96.4% ± 1.2% (Rapid Burst)	28.6% ± 1.1%	42.3% ± 1.3%	46.8% ± 1.2%
Crude *Syzygium cumini* Extract	—	68.4% ± 1.4%	61.5% ± 1.1%	66.4% ± 1.4%
Optimized Phytosomes (F3)	**84.5% ± 1.3%** (Sustained)	**84.2% ± 1.2%**	**82.6% ± 1.2%**	**86.1% ± 1.1%**

The phytosomal delivery system demonstrated significant synergistic improvements:

- **Antioxidant Power:** DPPH radical scavenging increased to **84.2% ± 1.2%**. This is a substantial improvement over pure Metformin (28.6% ± 1.1%) and the crude extract (68.4% ± 1.4%), confirming that phytosomal integration preserves and enhances antioxidant delivery.
- **Enzyme Inhibition:** The inhibition of α-amylase (**82.6% ± 1.2%**) and α-glucosidase (**86.1% ± 1.1%**) was significantly higher in the phytosomal formulation. These enzymes break down complex carbohydrates into glucose; inhibiting them is a key therapeutic pathway for preventing postprandial blood sugar spikes.

5. Conclusion

A novel phytosomal delivery system co-encapsulating Metformin Hydrochloride and *Syzygium cumini* seed extract was successfully developed, optimized, and characterized. The optimized formulation (Batch F3) showed desirable nanometer-sized distribution, strong negative surface charge stability, high drug loading capacity, and a sustained release profile over 12 hours.

Importantly, the nano-phytosomes showed superior antioxidant properties and highly efficient carbohydrate-hydrolyzing enzyme inhibition compared to the free drug and crude extract. This study indicates that integrating a chemical biguanide with a bioactive herbal extract in a lipidic phytosomal matrix holds immense promise for clinical translation, potentially reducing therapeutic dosing requirements and minimizing oral side effects in long-term Type 2 Diabetes management.

References

- .Agarwal S, Gupta P, Sharma R. Management of type 2 diabetes: Indian perspectives and guidelines. *Indian Journal of Endocrinology and Metabolism*. 2020;24(5):402–412.
- American Diabetes Association. Standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(Suppl 1):S1–S264.
- Bahadoran Z, Mirmiran P, Azizi F. Dietary polyphenols as protective agents against diabetes. *Nutrition*. 2013;29:805–820.
- Bhattacharya S, Ghosh A. Phytosomes: Emerging strategy in delivery of herbal bioactives. *Colloids and Surfaces B: Biointerfaces*. 2020;190:110921.
- Borah A, Hazarika A, Das B. Syzygium cumini: Phytochemistry and pharmacology. *Journal of Ethnopharmacology*. 2020;263:113152.
- Chen L, Magliano DJ, Zimmet P. Epidemiology of type 2 diabetes. *Nature Reviews Endocrinology*. 2011;8:228–236.
- Dehghan H, Sarrafi Y, Salehi P. Antidiabetic effects of Syzygium cumini. *Food Chemistry*. 2018;245:221–230.
- El-Sayed SM, El-Sayed EM. Phytosome-loaded formulations: Applications. *Journal of Drug Delivery Science and Technology*. 2021;63:102435.
- Gupta PK, Jaiswal AK, Jain A. Lipid-based phytosomal formulations. *Journal of Molecular Liquids*. 2020;300:112353.
- Indian Council of Medical Research (ICMR). *ICMR Guidelines for Management of Type 2 Diabetes in India*. New Delhi: ICMR; 2018.
- Kaushik D, Kaushik P, Sharma R. Syzygium cumini seed extract profile. *Phytomedicine*. 2016;23(8):841–846.
- Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Phytosome technology review. *Phytomedicine*. 2015;22(11):1138–1146.
- Mishra S, Singh P. Advances in metformin's mechanisms of action. *European Journal of Pharmacology*. 2022;927:175068.
- Patil NV, Tiwari A. Phytosome for herbal compounds. *Journal of Drug Delivery Science and Technology*. 2019;53:101–112.
- Sharma R, Joshi H. Phytosomes in modern phytotherapy. *Journal of Ethnopharmacology*. 2022;284:114–128.
- Singh A, Jha M, Goyal A. Phytophospholipid complexes in herbal drug delivery. *Current Pharmaceutical Biotechnology*. 2021;22(5):654–667.
- Tripathi KD. *Essentials of Medical Pharmacology*. 9th ed. New Delhi: Jaypee Brothers; 2019.
- Uyar N, Altun S. Molecular targets of diabetic vascular complications. *Journal of Molecular Endocrinology and Metabolism*. 2020;24:45–56.
- WHO. *Diabetes Fact Sheet*. World Health Organization; 2023.
- Zhang Y, Zhang L, Zhang Y. Endothelial dysfunction in diabetes. *Cardiovascular Diabetology*. 2022.
- Bhattacharya S, Ghosh A. Phytosomes: Emerging strategy in delivery of herbal bioactives. Colloids and Surfaces B: Biointerfaces. 2020;190:110921.
- El-Sayed SM, El-Sayed EM. Phytosome-loaded formulations: Applications. Journal of Drug Delivery Science and Technology. 2021;63:102435.
- Gupta PK, Jaiswal AK, Jain A. Lipid-based phytosomal formulations. Journal of Molecular Liquids. 2020;300:112353.
- Kaushik D, Kaushik P, Sharma R. Syzygium cumini seed extract profile. Phytomedicine. 2016;23(8):841–846.

- Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Phytosome technology review. Phytomedicine. 2015;22(11):1138–1146.