"Formulation and evaluation of (HPMC–EC) Microspheres loaded with Polyherbal extract"

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Abstract:

The shift toward polyherbal medicine is driven by lower side effects and synergistic benefits. However, herbal extracts often face issues with instability and rapid release. Polymer-based microspheres solve these problems by improving bioavailability, stability, enabling sustained delivery of bioactive compounds. The primary aim of this research was to formulate and evaluate mucoadhesive microspheres loaded with a polyherbal extract using a combination of Hydroxypropyl Methylcellulose (HPMC) and Ethyl Cellulose (EC). The objectives included optimizing the polymer-to-drug ratio, assessing the physical characteristics of the microspheres, and evaluating the *in vitro* release kinetics. The study utilized a polyherbal extract derived from a combination of botanicals known for their therapeutic properties i.e. *Momordica charantia* and *Aegle marmelos*. These plants were selected based on their high flavonoid and phenolic content, which contribute to significant antidiabetic as well as antioxidant and anti-inflammatory activities. **Material and Methods:** Microspheres were prepared using the solvent evaporation technique. HPMC was employed as the mucoadhesive polymer, while EC provided the sustained-release matrix. **Results:** The optimized formulation exhibited good entrapment efficiency (ranging from 65% to 76%) and a uniform spherical morphology.The study successfully created a stable HPMC–EC microsphere system for polyherbal extracts. By providing controlled release, this formulation can reduce dosing frequency and improve patient compliance, offering a standardized, modern platform for complex herbal delivery.

.**Keywords:** Polyherbal extract, *Momordica charantia*, *Aegle marmelos*, Microspheres, HPMC, Ethyl Cellulose, Solvent evaporation, Sustained release.

Introduction

Diabetes Mellitus (DM) is no longer merely a disorder; it is a global epidemic of the 21st century. It is a chronic metabolic disorder characterized by persistent hyperglycemia (elevated blood glucose levels) and long-term microvascular and macrovascular complications [1]. It arises from either a deficiency in insulin production, a resistance to the effects of insulin, or both. Since insulin is the primary hormone responsible for moving glucose from the bloodstream into the cells for energy, its dysfunction leads to a state of "starvation amidst plenty" for the body's tissues[2].

The condition is generally categorized into three main types:[3]

- **Type 1 Diabetes:** An autoimmune condition where the pancreas produces little to no insulin.

- **Type 2 Diabetes:** The most common form, characterized by insulin resistance, where the body's cells do not respond effectively to insulin, often linked to genetics and lifestyle factors.
- **Gestational Diabetes:** High blood sugar that develops during pregnancy and usually resolves after childbirth.

Microspheres are multiparticulate drug delivery systems (ranging from 1□ to 1000 □) that offer several advantages over traditional tablets or capsules [4]. They provide a high surface area-to- volume ratio, ensuring more predictable absorption. More importantly, they allow for controlled release, maintaining a steady plasma concentration of the drug and reducing the "peak-and-trough" effect often seen with conventional dosing [5]. The core of this thesis explores the interplay between two distinct polymers:

- Hydroxypropyl Methylcellulose (HPMC) and Ethyl Cellulose (EC). HPMC is a water-soluble polymer that acts as a "swelling agent." Upon contact with gastric fluid, it forms a gel layer that controls the initial entry of water into the microsphere. It ensures that the "loading dose" is delivered effectively.[6]
- Ethyl cellulose is a water-insoluble and pH-independent polymer that serves as the "rate-controlling membrane" or matrix. It prevents the microsphere from disintegrating too quickly, ensuring that the herbal extract is released slowly over an extended period (10–12 hours). By modulating the ratio of HPMC to EC, we can "tune" the release profile to match the metabolic needs of a diabetic patient.[6]

There is currently a lack of standardized, controlled-release polyherbal formulations in the market that combine the specific synergistic benefits of *M. charantia* and *A. marmelos*. Most available products are simple powders or aqueous extracts with poor shelf-stability and low patient compliance due to the bitter taste and frequent dosing requirements. This research proposes a Polyherbal Microsphere system that helps in masking the intensely bitter taste of *M. charantia*, protects the sensitive polyphenols of *A. marmelos* from oxidation and provides a sustained therapeutic effect, potentially allowing for "once-a-day" dosing[7].

Material and Methods:

1. Procurement and Authentication of Materials

The accuracy of any pharmaceutical research depends heavily on the quality and standardization of the raw materials.



- **Plant Material:** Dried *Momordica charantia* (Bitter Melon) fruits and *Aegle marmelos* (Bael) leaves were procured from the lab facilities of Oriental College of Pharmacy, Bhopal (M.P.). Authentication was performed to ensure the species' identity and to rule out adulteration.
- Polymers and Chemicals: All the chemicals are obtained from the lab facilities of Oriental College of Pharmacy, Bhopal (M.P.).
- **Ethyl Cellulose (EC):** Used as the hydrophobic, rate-controlling matrix polymer.
- **Hydroxypropyl Methylcellulose (HPMC):** Utilized as the hydrophilic, swellable polymer to modulate drug release.
- **Solvents:** Dichloromethane (DCM) and Ethanol (Analytical Grade) served as the primary and co-solvents.
- **Stabilizer:** Polyvinyl Alcohol (PVA) was employed as the emulsifying agent.
- **Water:** Freshly prepared double-distilled water was used throughout the study to prevent ionic interference.

2. Processing and Standardization of Plant Material [8]

- **Cleaning and Surface Decontamination**

The raw fruits of *M. charantia* and leaves of *A. marmelos* were first subjected to a rigorous washing process. Tap water was used to remove physical debris, followed by multiple rinses with distilled water to eliminate microbial load and surface contaminants.

- **Controlled Drying (Shade Drying)**

To preserve the integrity of thermolabile phytochemicals (such as charantin and various volatile oils), the materials were **shade-dried** at a controlled room temperature (25±2 °C). This slow drying process prevents the oxidative degradation that often occurs with rapid oven-drying, ensuring that the pharmacological potency of the extracts remains intact.

- **Size Reduction and Sieve Analysis**

After reaching a constant weight, the dried materials were pulverized using a high-speed mechanical electrical grinder. The resulting coarse powder was passed through a **40-mesh sieve**.

- **Rationale:** A 40-mesh size provides an optimal surface-area-to-volume ratio. If the powder is too coarse, solvent penetration is poor; if too fine, the powder may clump during extraction, creating "dead zones" where the solvent cannot reach.

3. Extraction Protocol [9]

- **Rationale for the Hydroalcoholic Solvent System**

A binary solvent system of Ethanol and Distilled Water (50:50 v/v) was formulated. Ethanol is highly effective at dissolving intermediate-polarity compounds like alkaloids and flavonoids. Water ensures the extraction of highly polar constituents, tannins, and saponins. This synergistic approach ensures an "exhaustive extraction," capturing the full spectrum of antidiabetic constituents present in both plants.

- **The Soxhlet Extraction Process[10]**

The extraction was conducted using a standard Soxhlet apparatus, a method chosen for its ability to recycle the solvent and maintain a high concentration gradient.

1. **Loading:** 50 grams of the 40-mesh powder was packed into a cellulose thimble.
2. **Cycle Dynamics:** 300 mL of the 50:50 hydroalcoholic mixture was heated in a round-bottom flask. As the solvent boiled, the vapors rose into the condenser, dripped onto the plant material, and eventually siphoned back into the flask once the chamber was full.
3. **Duration:** The process was maintained for 6–8 hours. Completion was visually confirmed when the solvent in the siphon tube became completely colorless, indicating that no further solutes were being extracted.
4. **Concentration:** The resulting liquid was filtered and concentrated using a rotary evaporator or a water bath at low temperature to obtain a semi-solid crude extract.

4. Analytical Pre-formulation: [11]

UV-Visible Spectroscopy

To establish a baseline for quantification and to confirm the presence of specific markers, absorption maxima (□max) were determined.

- **Procedure:** 10 mg of each extract was dissolved in 100 mL of the solvent to create a stock solution. This was further diluted to reach a concentration of 10□/ml.
- **Scanning:** The solutions were scanned using Shimadzu UV-1700 double-beam spectrophotometer across the UV-Visible range of 300–700 nm.
- **Results:**
    - *M. charantia* displayed a characteristic peak at ~408 nm.
    - *A. marmelos* displayed a characteristic peak at ~276 nm. These values were recorded as the standard wavelengths for all subsequent entrapment efficiency and *in vitro* drug release calculations.

5. Formulation of Microspheres[12-13]

- **The Solvent Diffusion-Evaporation Technique:** This method was selected because it allows for the encapsulation of both hydrophilic and hydrophobic substances within a polymeric shell.
- **Preparation of the Organic Phase:** Accurately weighed amounts of the herbal extracts (25 mg each) and the polymer blend (HPMC and EC) were dissolved in a mixture of Ethanol and Dichloromethane (1:2 v/v). DCM is the primary solvent for Ethyl Cellulose. Ethanol acts as a co-solvent to ensure HPMC and the herbal extracts remain in a homogenous, clear solution, preventing premature precipitation. The study utilized five distinct batches (F1–F5) to evaluate the impact of the HPMC to EC ratio on the microsphere characteristics.[14]

Table No 1: Formulation of microspheres in different ratios

Batch Code	Polymer Ratio (HPMC:EC)	M. charantia Extract (mg)	A. marmelos Extract (mg)	Solvent Ratio (EtOH:DCM)
F1	1 : 0.5	25	25	1 : 2
F2	1 : 1.0	25	25	1 : 2
F3	1 : 1.5	25	25	1 : 2
F4	1 : 2.0	25	25	1 : 2
F5	1 : 2.5	25	25	1 : 2

- **Aqueous Phase Preparation:** An external phase was prepared by dissolving 1% w/v Polyvinyl Alcohol (PVA) in distilled water. PVA serves as a surfactant, preventing the organic droplets from merging.
- **Emulsification:** The organic drug-polymer solution was introduced into the aqueous phase in a slow, steady stream using a syringe.
- **Stirring:** The system was stirred continuously for 3 hours using a mechanical stirrer at an ambient temperature of 27±2°C.
- **Mechanism of Formation:** As stirring progressed, Ethanol diffused into the water, and the volatile DCM evaporated into the air. This forced the polymers to precipitate around the herbal extracts, hardening the droplets into solid, spherical microspheres.

Results:

Evaluation of Prepared Microspheres

The formulated microspheres were subjected to the following physicochemical and micromeritic evaluations to determine their suitability for oral delivery.

1. Preformulation studies

Preformulation studies are essential to ensure stability, efficacy, and reproducibility of the final dosage form. These studies typically involve evaluating the physicochemical properties of the plant extracts such as colour, taste, odour, solubility.

Parameter	*Momordica charantia*	*Aegle marmelos*
Colour	Greenish-brown	Dull green to yellowish-green
Odour	Characteristic, slightly unpleasant, and pungent	Characteristic aromatic and pleasant balsamic odour
Taste	Extremely bitter	Slightly bitter and slightly pungent.
Solubility	Soluble in water, ethanol, methanol,etc. solubility low in chloroform and petroleum ether,etc.	Soluble in water, ethanol, methanol,etc. solubility low in chloroform and petroleum ether,etc.

Table No 2: Preformulation studies of plants.

2. Percentage Yield

The practical yield of the microspheres was calculated to determine the efficiency of the solvent diffusion-evaporation method. It is the ratio of the weight of the dried microspheres recovered to the total initial weight of the drugs and polymers used in the formulation.

Table No 3: Percentage yield of microspheres

Formulation	Percentage yield
F1	63.83±0.25
F2	65.59±0.28
F3	73.81±0.14
F4	69.13±0.18
F5	68.10±0.32

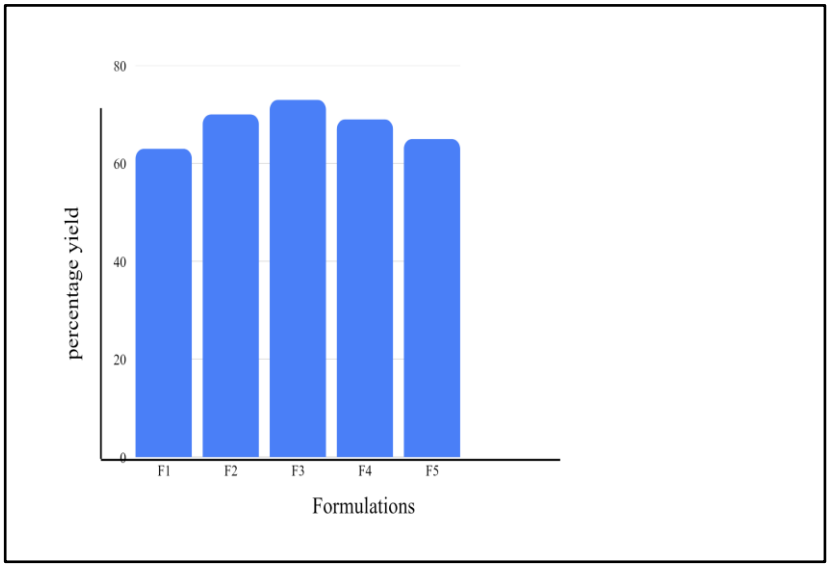


Figure no 1: Percentage Yield of formulations

3. Particle Size Distribution

The mean particle size and size distribution were determined using optical microscopy. A small quantity of microspheres was suspended in a non-solvent and spread on a glass slide. The diameters of at least 100 particles were measured using a calibrated ocular micrometer to ensure uniformity and to understand the impact of stirring speed on sphere dimensions.

4. Drug Loading and Encapsulation Efficiency

To determine the drug content, a known weight of microspheres was crushed and dissolved in a suitable solvent (Ethanol/Water). After filtration and appropriate dilution, the concentration was analyzed via **UV-Visible Spectroscopy**.

- **Drug Loading:** Represents the ratio of the mass of the drug actually trapped to the total mass of the microspheres.
- **Encapsulation Efficiency:** Measures the percentage of the initial drug that was successfully entrapped within the polymer matrix.

Table No 4:Drug entrapment percentage of microspheres:

Formulation	Drug entrapment (% w/w) of prepared microsphere
F1	69.98±0.62
F2	71.26±0.58
F3	76.03±0.23
F4	69.12±0.65
F5	65.58±0.48

*Average of three determination (n=3)

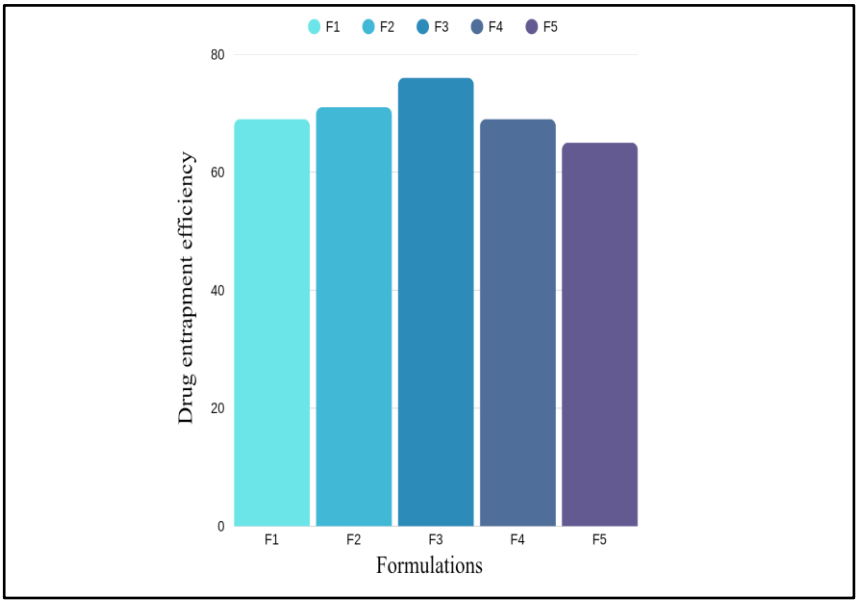


Figure no 2:Drug entrapment efficiency of formulations

6. In-Vitro Drug Release Studies

This study simulates the release of the herbal extracts from the microspheres into the gastrointestinal tract. For this, USP Type II (paddle type) dissolution apparatus is used. A known amount of microspheres (equivalent to a standard dose of the extract) is placed in 900 mL of dissolution medium. To simulate the GI transit, the study is often conducted in 0.1 N HCl (pH 1.2) for the first 2 hours and then replaced with Phosphate Buffer (pH 6.8) for the remaining 10–20 hours. The temperature is maintained at expression 37±0.5°C with a constant stirring speed. At specific time intervals, 5 mL of the sample is withdrawn and replaced with fresh medium to maintain sink conditions.

Table No 5: Percentage of drug release:

Time	Percentage of Drug Release				
(in hrs)	F1	F2	F3	F4	F5
0.5	15.65	18.23	20.23	-	-
1	23.32	25.65	25.65	20.13	-
2	29.65	32.34	35.65	31.98	29.57
4	37.01	40.66	45.56	44.05	38.84
8	43.96	51.30	56.83	52.09	46.23
10	50.67	58.97	63.23	65.33	53.89
12	61.70	65.78	79.56	73.32	69.83

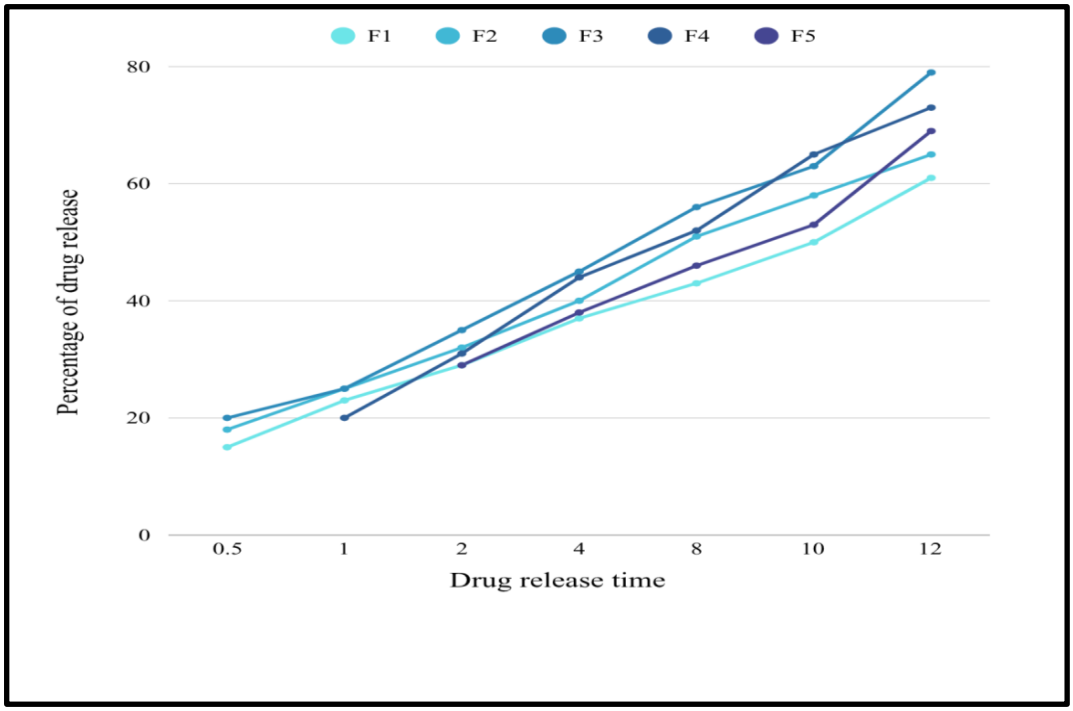


Figure no 3: Drug release of Formulations

Summary:

The prepared microspheres exhibited desirable physicochemical properties, including excellent flow characteristics and high encapsulation efficiency, indicating suitability for oral administration. In-vitro drug release studies demonstrated a controlled and sustained release pattern. Overall, this dual-herb microsphere formulation represents a promising and stable approach for sustained antidiabetic therapy. By combining the insulin-mimetic activity of *Momordica charantia* with the pancreatic protective effects of *Aegle marmelos*, the system offers a synergistic therapeutic advantage in the management of chronic hyperglycemia. However, further in-vivo pharmacokinetic and pharmacodynamic studies are required to validate its clinical efficacy and establish its potential as an alternative to conventional treatment strategies.

Conclusion:

The study successfully developed stable HPMC–Ethyl Cellulose microspheres loaded with Momordica charantia and Aegle marmelos extracts using the solvent diffusion-evaporation technique. The formulation demonstrated high entrapment efficiency and a sustained release profile, effectively preserving the bioactive phytoconstituents. These results indicate that the microsphere system is a viable and efficient vehicle for enhancing the delivery and therapeutic potential of herbal antidiabetic agents

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