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FORMULATION AND CHARACTERIZATION OF CANNABIDIOL SUSTAINED RELEASE BLEND MICROSPHERES

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Abstract:
The present study aimed to formulate and characterize sustained release blend microspheres of cannabidiol using the solvent evaporation technique. Cannabidiol, a poorly water-soluble drug with low bioavailability, requires an effective delivery system to achieve prolonged therapeutic action. In this study, microspheres were prepared using different ratios of hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and guar gum to evaluate their influence on drug release and formulation characteristics. A total of six formulations (F1–F6) were developed and evaluated for percentage yield, drug entrapment efficiency, buoyancy, particle size, zeta potential, and in-vitro drug release. The percentage yield ranged from 72.85% to 82.94%, while drug entrapment efficiency varied between 69.85% and 81.36%. Among all formulations, F5 exhibited the highest yield (82.94%) and entrapment efficiency (81.36%), along with superior buoyancy (81.15%) and shortest floating lag time (50 seconds). The optimized formulation showed uniform particle size distribution and good stability as confirmed by zeta potential analysis. In-vitro drug release studies demonstrated sustained release of cannabidiol over 12 hours, with formulation F5 releasing 98.85% of the drug. Release kinetics indicated that the formulation followed zero-order and Korsmeyer–Peppas models, suggesting a non-Fickian diffusion mechanism. Stability studies confirmed that the optimized formulation remained stable under accelerated conditions without significant changes in physicochemical properties. In conclusion, the developed sustained release blend microspheres of cannabidiol showed promising results in terms of controlled drug release, enhanced stability, and improved drug encapsulation, making them a potential candidate for effective drug delivery.

Keywords: *Cannabidiol, Sustained release, Microspheres, Solvent evaporation, HPMC, Ethyl cellulose, Guar gum, Drug entrapment, Buoyancy, Release kinetics.*

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INTRODUCTION:

In recent years, controlled and sustained drug delivery systems have gained significant attention in pharmaceutical research due to their ability to maintain consistent drug levels, improve therapeutic efficacy, and enhance patient compliance [1].

Conventional dosage forms often lead to fluctuations in plasma drug concentration, resulting in reduced effectiveness and increased side effects. Sustained release systems overcome these limitations by providing a controlled and prolonged release of drugs over an extended period[2] .

Cannabidiol (CBD), a non-psychoactive constituent of *Cannabis sativa*, has attracted considerable interest owing to its wide range of therapeutic applications, including analgesic, anti-inflammatory, anticonvulsant, anxiolytic, and neuroprotective effects. Despite its promising pharmacological profile, cannabidiol exhibits poor aqueous solubility, low oral bioavailability, and extensive first-pass metabolism, which limit its clinical effectiveness. Therefore, the development of an efficient drug delivery system is essential to enhance its bioavailability and therapeutic performance [3].

Microspheres are one of the most promising sustained release drug delivery systems. They are small, spherical particles that can encapsulate drugs within polymeric matrices, allowing controlled drug release and improved stability. Microspheres offer several advantages, such as reduced dosing frequency, minimized side effects, targeted delivery, and improved patient adherence. Blend microspheres, prepared using a combination of polymers, provide better control over drug release profiles by modulating polymer properties such as degradation rate, swelling behavior, and permeability [4].

Various polymers, both natural and synthetic, are used in the formulation of microspheres to achieve sustained drug release. Polymers such as ethyl cellulose, polyvinyl alcohol (PVA), and other biodegradable materials play a essential role in controlling drug release kinetics. The selection and combination of suitable polymers are significant in designing an effective sustained release system for poorly soluble drugs like cannabidiol [5-6].

The present study focuses on the formulation and characterization of cannabidiol sustained release blend microspheres using appropriate polymers. The microspheres are prepared using suitable techniques such as solvent evaporation or emulsion methods, followed by evaluation of parameters including particle size, drug entrapment efficiency, surface morphology, and in vitro drug release. The developed system aims to provide prolonged drug release, improved bioavailability, and enhanced therapeutic efficacy of cannabidiol, making it a promising approach for advanced drug delivery applications.

MATERIAL AND METHODS:

Material

Cannabidiol was used as the active pharmaceutical ingredient for the preparation of sustained release microspheres. Hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and guar gum were used as polymers to control drug release and form the microsphere matrix. Polyvinyl alcohol (PVA) was employed as a stabilizer and emulsifying agent in the external aqueous phase. Ethanol and dichloromethane were used as organic solvents for dissolving the drug and polymers during the preparation process. Distilled water was used for the preparation of aqueous solutions and washing of microspheres. All chemicals and reagents used in the study were of analytical grade and were utilized as received without further purification.

Methods

Preparation of sustained release blend microsphere of Cannabidiol

Sustained release microspheres of Cannabidiol were prepared using the solvent evaporation technique**,** employing different ratios of HPMC, EC, and guar gum as shown in Table 1. The polymer composition (F1–F6) was varied systematically to evaluate its influence on particle formation, entrapment efficiency, buoyancy, and drug release [7].

Table 1: Formulations of sustained release microspheres of Cannabidiol

S. No.	Formulation Code	Cannabidiol (mg)	HPMC (mg)	EC (mg)	Guar gum (mg)
1.	F1	50	50	100	-
2.	F2	50	50	150	-
3.	F3	50	50	200	-
4.	F4	50	100	50	10
5.	F5	50	150	50	20
6.	F6	50	200	50	30

For each formulation (F1–F6), Cannabidiol (50 mg) along with the corresponding quantities of HPMC, EC, and guar gum (as listed in Table 1) were accurately weighed. The weighed components were transferred into a clean beaker, followed by the addition of a solvent mixture consisting of ethanol and dichloromethane in a 1:2 ratio. Continuous stirring was applied to obtain a uniform and homogenous drug–polymer solution. This organic phase was then introduced slowly in a thin stream into 1% w/v Polyvinyl Alcohol (PVA) aqueous solution, serving as the external phase. Emulsification was carried out at a controlled stirring speed of 500 rpm and temperature of 27 ± 2°C. The system was maintained under constant stirring for 3 hours, allowing complete evaporation of the organic solvents and formation of microspheres. During this period, floating sustained-release microspheres gradually formed at the surface, whereas non-floating particles settled at the bottom. The buoyant microspheres were carefully collected by decantation, while non-floating particles were discarded to ensure consistent floating behavior. The collected microspheres were washed thoroughly with distilled water to remove residual PVA and impurities. The washed microspheres were then dried at 40 ± 2°C in a hot air oven overnight to obtain free-flowing sustained-release microspheres. The dried microspheres were stored in a desiccator until further evaluation.

Evaluation of microspheres

Percentage yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres [8]

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug entrapment

The various formulations of the sustained release microspheres were subjected for drug content. 10 mg of sustained release microspheres from all batches were accurately weighed and crushed [9]. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method at 222nm.

Floating behavior

Ten milligrams of the sustained release floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer [10]. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement [11].

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate [12].

***In-vitro* release studies**

The *in vitro* drug release rate from sustained release microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly [13]. A weighed amount of sustained release microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 222nm to determine the concentration of drug present in the dissolution medium.

RESULTS AND DISCUSSION:

The present study was focused on the formulation and evaluation of sustained release blend microspheres of cannabidiol using the solvent evaporation technique. Different polymer combinations of HPMC, ethyl cellulose (EC), and guar gum were employed to investigate their influence on microsphere characteristics, as shown in Table 7.1.

The percentage yield of all formulations (Table 2) ranged from 72.85% to 82.94%, indicating satisfactory production efficiency of the solvent evaporation method. Among all batches, formulation F5 exhibited the highest yield (82.94%), which may be attributed to the optimal polymer concentration and improved matrix formation that minimized drug loss during processing. Lower yields in other formulations might be due to polymer loss during washing and handling steps.

Drug entrapment efficiency results (Table 3) showed values between 69.85% and 81.36%, indicating effective encapsulation of cannabidiol within the polymer matrix. Formulation F5 again demonstrated the highest entrapment efficiency (81.36%), suggesting that the combination of higher HPMC and guar gum concentrations with EC provided a dense polymer network, reducing drug diffusion into the external phase during preparation. In contrast, formulations with lower polymer concentration showed comparatively reduced entrapment due to weaker matrix formation.

The buoyancy study (Table 4) revealed that all formulations exhibited good floating behavior, which is essential for gastric retention and sustained drug release. The floating lag time ranged from 50 to 88 seconds, while percentage buoyancy varied from 72.86% to 81.15%. Formulation F5 showed the shortest floating lag time (50 seconds) and highest buoyancy (81.15%), indicating rapid and prolonged floating ability. This may be due to the presence of guar gum and optimized polymer ratios, which enhance matrix integrity and reduce density, allowing the microspheres to remain buoyant for extended periods.

The particle size analysis of the optimized formulation F5 (Figure 1) confirmed the formation of uniform microspheres within the desired size range, which is crucial for controlled drug release. The zeta potential value (Figure 2) indicated good stability of the microspheres, suggesting minimal aggregation due to sufficient surface charge.

In-vitro drug release studies (Table 5) demonstrated that formulations F1–F3 showed a faster drug release due to lower polymer viscosity and absence of guar gum, whereas formulations F4–F6 exhibited a more sustained release pattern. Among all, formulation F5 showed a controlled and prolonged release profile, releasing 98.85% drug over 12 hours. The initial burst release was minimized, and a steady release pattern was achieved, indicating the effectiveness of the polymer blend in controlling drug diffusion.

The release kinetics analysis (Table 6) showed that formulation F5 followed zero-order kinetics (R^2 = 0.9928), indicating a constant drug release over time. The high correlation with the Korsmeyer–Peppas model (R^2 = 0.9887) suggests that the drug release mechanism follows non-Fickian (anomalous) transport, involving both diffusion and polymer relaxation.

The accelerated stability study of the optimized formulation F5 (Table 7) demonstrated that there were no significant changes in appearance, drug content, dissolution, or assay values over a period of 3 months under stress conditions (40 ± 2°C / 75 ± 5% RH). This indicates that the formulation is stable and maintains its integrity and performance over time.

Formulation F5 was identified as the optimized formulation based on its highest yield, superior entrapment efficiency, excellent buoyancy, controlled drug release, and good stability profile. The combination of HPMC, EC, and guar gum proved effective in developing sustained release microspheres of cannabidiol, making it a promising system for prolonged drug delivery and improved therapeutic efficacy.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield (%)
1	F1	72.85 ± 0.52
2	F2	75.48 ± 0.41
3	F3	74.12 ± 0.38
4	F4	77.26 ± 0.55
5	F5	82.94 ± 0.87
6	F6	75.96 ± 0.44

Table 3: Drug entrapment for different formulations

S. No.	Formulation	Drug Entrapment (% w/w) of Prepared Microspheres
1	F1	69.85 ± 0.58
2	F2	72.48 ± 0.34
3	F3	71.64 ± 0.69
4	F4	75.12 ± 0.81
5	F5	81.36 ± 0.72
6	F6	72.95 ± 0.41

Table 4: Percentage Buoyancy and floating lag time of microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy (%)
F1	88 ± 4	75.82 ± 0.52
F2	78 ± 5	73.94 ± 0.68
F3	70 ± 3	72.86 ± 0.59
F4	73 ± 4	74.12 ± 0.46
F5	50 ± 2	81.15 ± 0.71
F6	67 ± 6	73.48 ± 0.63

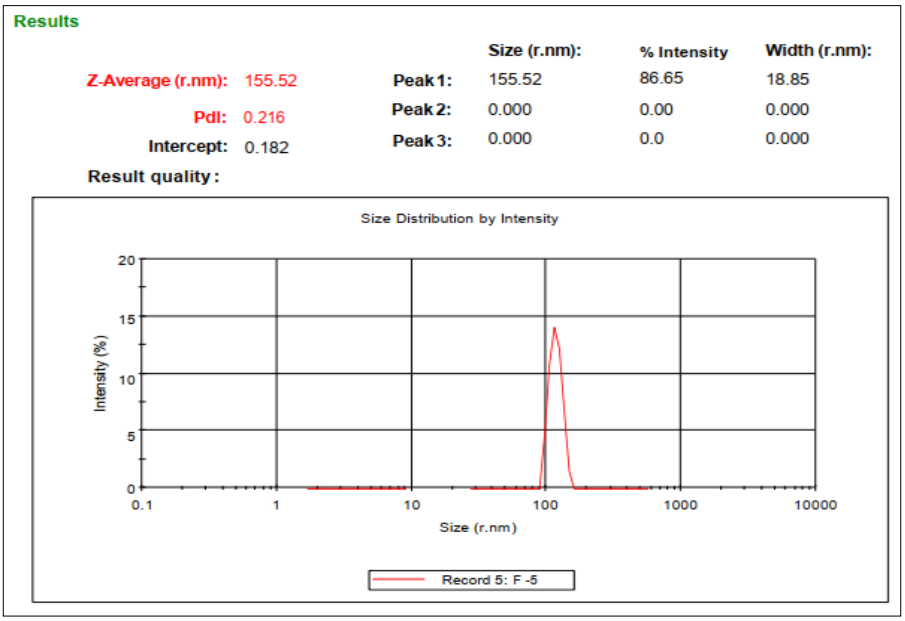

Figure 1: Particle size data of optimized microsphere formulation F5

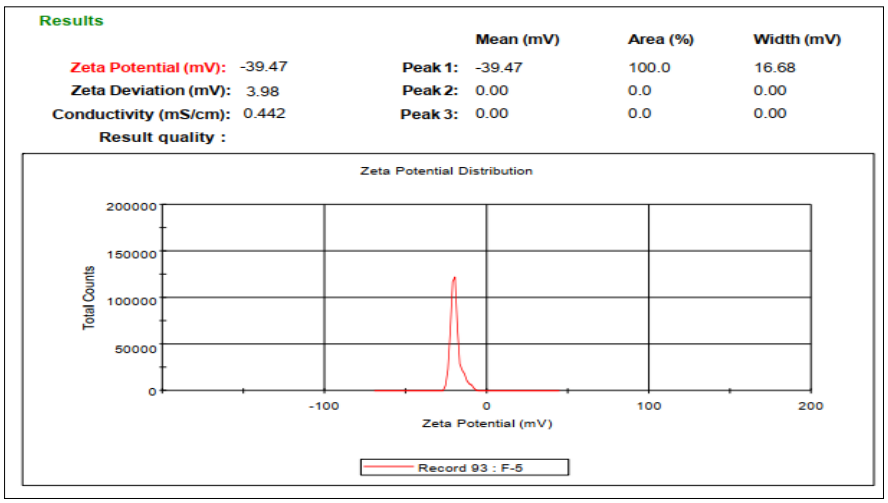

Figure 2: Zeta potential data of sustained release microsphere F5

Table 5: Release Study data of formulation F1-F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0.5	38.45	42.15	40.25	20.45	15.85	11.95
1	52.35	53.65	49.75	33.85	20.45	18.25
2	60.25	65.35	61.45	44.25	32.15	28.45
4	72.65	76.25	70.15	56.85	42.35	39.25
6	83.25	85.95	80.65	69.45	59.85	52.75
8	90.45	94.25	87.95	86.25	71.45	66.85
10	97.15	98.35	96.85	96.45	80.75	75.65
12	98.65	99.15	97.85	97.95	98.85	80.95

Table 6: Comparative study of regression coefficient for selection of optimized Formulation F5

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.9928	0.7400	0.9794	0.9887

Table 7: Accelerated Stability Study of Optimized Formulation F5 (40 ± 2°C / 75 ± 5% RH)

S. No.	Parameter	Initial	After 1 Month	After 2 Months	After 3 Months
1	Appearance	Smooth, uniform, no color change	No change	No change	No change
2	Drug Content (%)	98.45 ± 0.32	98.12 ± 0.28	97.86 ± 0.35	97.54 ± 0.30
3	Dissolution (%)	96.72 ± 0.41	96.30 ± 0.38	95.84 ± 0.40	95.42 ± 0.36
4	Assay (%)	99.10 ± 0.27	98.76 ± 0.25	98.33 ± 0.29	98.05 ± 0.31

CONCLUSION:

The present study successfully formulated sustained release blend microspheres of cannabidiol using the solvent evaporation technique. The prepared formulations exhibited satisfactory physicochemical properties, including good percentage yield, efficient drug entrapment, and excellent buoyancy. Among all formulations, F5 was identified as the optimized formulation due to its highest yield, maximum entrapment efficiency, superior floating behavior, and controlled drug release over 12 hours. The release kinetics followed zero-order and non-Fickian diffusion mechanisms, indicating a combination of diffusion and polymer relaxation. Stability studies confirmed that the optimized formulation remained stable under accelerated conditions. The developed microspheres offer a promising approach for sustained delivery of cannabidiol with improved therapeutic efficacy and patient compliance.

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