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FORMULATION AND EVALUATION OF FISETIN LOADED MICROSPHERES

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ABSTRACT

The present study was aimed at the formulation and evaluation of fisetin-loaded microspheres using the emulsion solvent evaporation technique. Fisetin, a bioactive flavonoid with significant antioxidant and anti-inflammatory properties, suffers from poor aqueous solubility and low bioavailability, limiting its therapeutic application. To overcome these limitations, microspheres were prepared using ethyl cellulose as a polymer, dichloromethane as a solvent, liquid paraffin as the external phase, and Span 80 as a surfactant. The prepared microspheres were evaluated for percentage yield, swelling index, solubility profile, particle size, FTIR compatibility, and in vitro drug release. The formulation showed a satisfactory percentage yield of 87.66% and a swelling index of 2.35%, indicating good stability. FTIR analysis confirmed the absence of significant drug-polymer interaction. The calibration curve exhibited good linearity, confirming analytical reliability. In vitro dissolution studies revealed sustained drug release from microspheres (75% in 12 hours) compared to pure fisetin (38%), demonstrating improved release characteristics. The study concludes that microsphere formulation is an effective approach to enhance the solubility, stability, and controlled release of fisetin, thereby improving its therapeutic potential.

KEYWORDS: Fisetin, Microspheres, Emulsion Solvent Evaporation, Ethyl Cellulose, Controlled Release, Drug Delivery System, FTIR, Dissolution Study, Bioavailability Enhancement.

INTRODUCTION

Fisetin is a naturally occurring flavonoid belonging to the polyphenolic class of compounds, commonly found in fruits and vegetables such as strawberries, apples, grapes, and onions. It has gained considerable attention due to its wide range of pharmacological activities, including antioxidant, anti-inflammatory, anticancer, and neuroprotective effects. These properties make fisetin a promising candidate for the treatment and prevention of various chronic diseases.[1,2]

Despite its therapeutic potential, the clinical application of fisetin is significantly limited due to its poor aqueous solubility and low oral bioavailability. It undergoes rapid metabolism and elimination, resulting in reduced systemic availability and diminished therapeutic efficacy. These limitations necessitate the development of advanced drug delivery systems to improve its pharmacokinetic profile.[3,4]

Flavonoids like fisetin are also prone to degradation under physiological and environmental conditions such as light, heat, and oxidation. This instability further reduces their effectiveness when administered through conventional dosage forms. Therefore, protecting fisetin from degradation while enhancing its stability is a critical challenge in formulation development.[5,6]

Microspheres are multiparticulate drug delivery systems consisting of small spherical particles, typically ranging from 1 to 1000 μm in size. They are widely used to encapsulate drugs within a polymeric matrix, offering protection from environmental degradation and enabling controlled drug release. Microspheres have emerged as an effective strategy for improving the delivery of poorly soluble drugs.[7,8]

The use of microspheres provides several advantages such as improved bioavailability, sustained release, reduced dosing frequency, and minimized side effects. They also allow for uniform distribution in the gastrointestinal tract and can be designed for site-specific delivery. These features make microspheres highly suitable for delivering bioactive compounds like fisetin.[9,10]

Various techniques are employed for the preparation of microspheres, including solvent evaporation, emulsification, spray drying, and coacervation. Among these, solvent evaporation is one of the most commonly used methods due to its simplicity and ability to produce uniform particles with high drug entrapment efficiency.[11,12]

The selection of polymers plays a crucial role in determining the characteristics of microspheres. Natural polymers such as chitosan and sodium alginate, as well as synthetic polymers like poly(lactic-co-glycolic acid) (PLGA), are widely used due to their biocompatibility, biodegradability, and controlled release properties. The polymer-drug interaction significantly influences the release behavior of the encapsulated drug.[13,14]

Encapsulation of fisetin into microspheres can enhance its solubility and stability by protecting it from degradation and improving its dispersion in biological fluids. This approach also allows for sustained release of fisetin over an extended period, thereby maintaining therapeutic drug levels and improving patient compliance.[15,16]

Evaluation of microspheres is essential to ensure their quality and performance. Key parameters such as particle size, surface morphology, drug entrapment efficiency, swelling behavior, and in vitro drug release profile are commonly studied. These parameters help in optimizing the formulation and predicting its in vivo behavior.[17,18]

In addition to physicochemical evaluation, stability studies are important to assess the shelf life and storage conditions of the formulated microspheres. Factors such as temperature, humidity, and light exposure can affect the stability of the formulation and must be carefully monitored during development.[19,20]

The present study focuses on the formulation and evaluation of fisetin-loaded microspheres using suitable polymers and preparation techniques. The objective is to enhance the solubility, stability, and bioavailability of fisetin while

achieving controlled drug release. Such a formulation holds significant potential for improving the therapeutic efficacy of fisetin in pharmaceutical applications.[21–25]

METHODOLOGY

S. No.	Ingredients	Quantity	USE
1.	Ethyl Cellulose	2 gm	Polymer
2.	Dichloromethane	30 ml	Solvent
3.	Fisetin	1 gm	API
4.	Liquid Paraffin	200 ml	Droplet Formation
5.	Span 80	4 ml	Surfactant

Method: *Emulsion Solvent Evaporation Technique.*

- Drug and polymer are dissolved in organic solvent.
- The solution is emulsified into an aqueous phase.
- Solvent is evaporated under continuous stirring.
- Microspheres are collected, washed and dried.

Formulation of Fisetin-Loaded Ethyl Cellulose
Microspheres by Solvent Evaporation Technique
(Single Emulsion O/W Method)

Principle

The solvent evaporation technique involves dissolving the drug and polymer in a volatile organic solvent and emulsifying this organic phase into an aqueous phase containing a stabilizer. Upon evaporation of the organic solvent, solid polymeric microspheres entrapping the drug are formed.

PROCEDURE

Preparation of Organic Phase

Accurately weighed ethyl cellulose (2 gm) was dissolved in 30 mL of dichloromethane (DCM) or ethyl acetate. 1 gm Fisetin was added to the polymer solution at a drug-to-polymer ratio of 1:5 (w/w). The mixture was stirred until a clear and homogeneous organic solution was obtained.

Preparation of Aqueous Phase

An aqueous solution of span 80 (1–2% w/v) was prepared by dissolving span 80 in liquid paraffin (200 mL) with gentle heating. The solution was allowed to cool to room temperature before use.

Emulsification (Formation of O/W Emulsion)

The organic phase containing ethyl cellulose and fisetin was slowly added dropwise into the aqueous span 80 solution under high-speed homogenization at 1000–1500 rpm for 1–3 hours. This resulted in the formation of a stable oil-in-water (O/W) emulsion.

Solvent Evaporation

The formed emulsion was stirred continuously at room temperature using a magnetic stirrer for 3–4 hours to allow complete evaporation of the organic solvent. Solvent evaporation led to hardening of the microspheres.

Collection and Washing of Microspheres

The hardened microspheres were collected by filteration and washed three times with n-hexane to remove residual span 80 and unentrapped drug.

Drying and Storage

The microspheres were dried using vacuum drying. The dried formulation was stored in a desiccator at room temperature until further evaluation.

Since fisetin is lipophilic, a single emulsion (O/W) solvent evaporation technique is sufficient and a double emulsion (W/O/W) method is not required. Reference: Wu J. et al. (2023)

RESULT

1. Percentage yield of the microsphere

The percentage yield of the microsphere was evaluated by using the ratio of practical yield and theoretical yield. Practical yield is the weight of the microsphere obtained. Total weight of the raw materials is theoretical yield.

Percent yield = Practical yield / Theoretical yield x 100

Percentage yield = 2.63/3 = 0.8766 x 100 = 87.66 %

2. Swelling index

10 mg of fisetin microsphere was added into 100 ml of phosphate buffer solution (pH 6.8) for 24 hours swelling index was measured using formula.[13] Swelling index = (Wv-Wi/Wi) X 100 Where, Wv represents weight of microspheres after 24 hrs Wi represents initial weight of microspheres. The swelling index of fisetin microsphere is found to be 2.35%

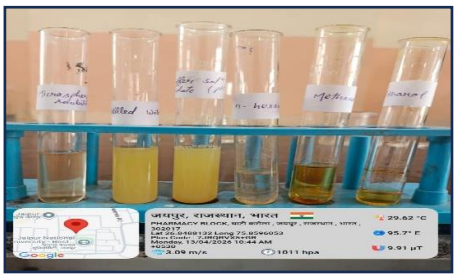
3. Solubility of Fisetin

The ability of the drug Fisetin incorporated within the microsphere formulation to dissolve in a given solvent or dissolution medium (usually aqueous media such as buffer solutions).

It indicates how much Fisetin is released and dissolved from the microspheres into the surrounding fluid over time.

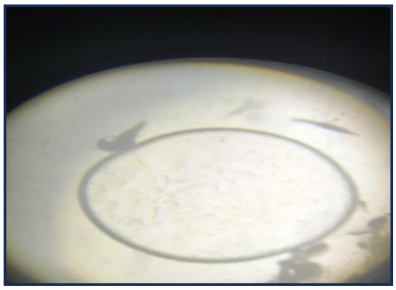
Solubility Profile of Fisetin

- Methanol → Freely Soluble
- Ethanol → Soluble
- Buffer Solution → Slightly Soluble
- Distilled Water → Very Slightly Soluble
- N-Hexane → Practically Insoluble



4. Optical microscopy study

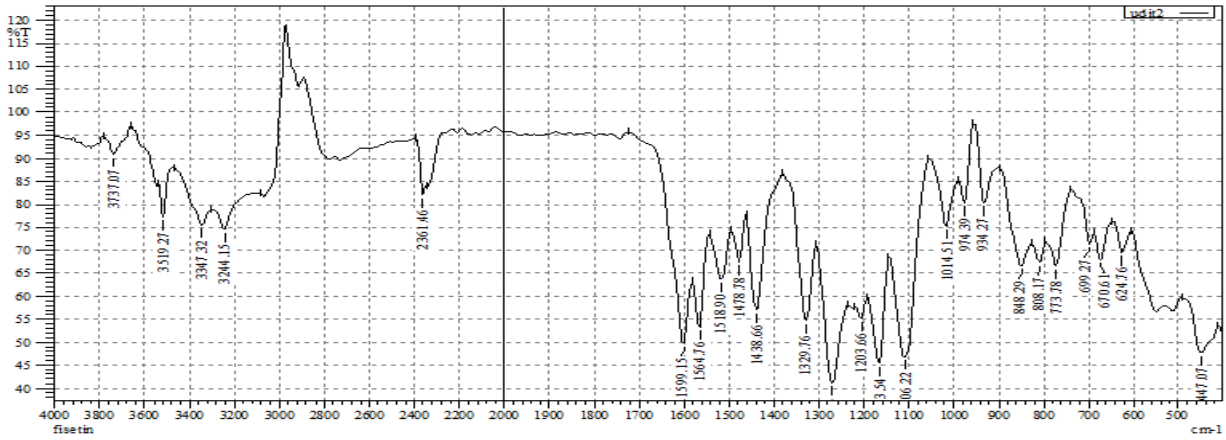
Optical microscopy study of Fisetin microspheres is the technique of examining the prepared microspheres under a light microscope to determine their particle size, shape and surface characteristics.



5. Fourier Transform Infrared Spectroscopy (FTIR) Study

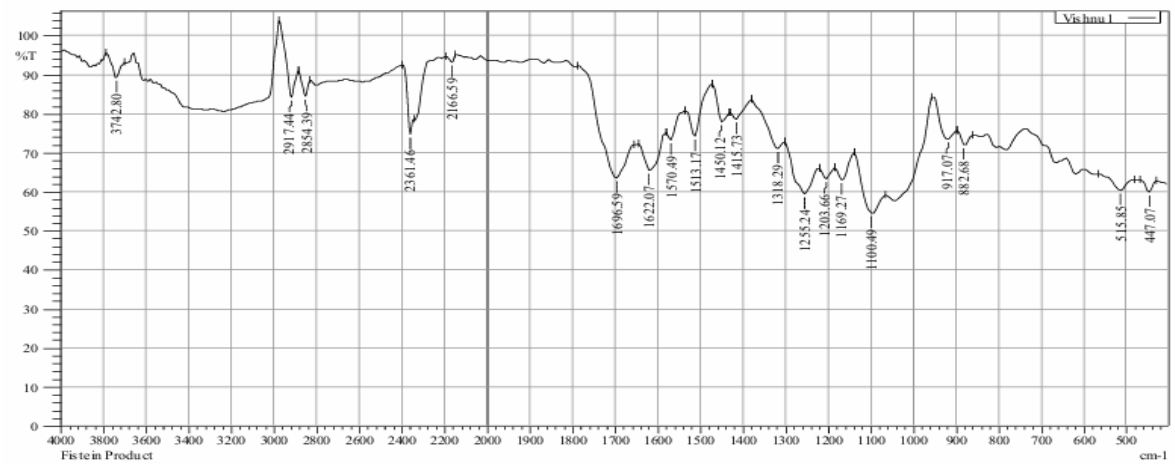
FTIR was used to determine the chemical interactions between the drug molecule and other ingredients used in the microsphere preparation.

- Clean the ATR crystal with isopropanol or ethanol and dry it.
- Take a background scan.
- Put a small amount powder on the crystal.
- Press the powder gently with the pressure arm for good contact.
- Scan the sample (usual settings: 4000–400 cm^{-1}, 4 cm^{-1} resolution, 16–64 scans).
- Clean the crystal again after use.



FTIR of Fisetin Drug

- (4000–3000 cm^{-1}) 3737 cm^{-1}-Free –OH stretching (alcohol/phenol, non H-bonded)
- 3000–2800 cm^{-1}- (C–H region)Strong peaks around
- 2950–2850 cm^{-1} - Aliphatic C–H stretching
- (1800–1500 cm^{-1})1599 cm^{-1} - C=C stretching
- 808 cm^{-1} → Aromatic C–H bending



FTIR of Fisetin Loaded Microsphere

Peak (cm^{-1})	Functional Group	Interpretation
~3742 cm^{-1}	O–H stretching	Phenolic hydroxyl groups of fisetin and hydrogen bonding
~3017–2854 cm^{-1}	C–H stretching	Aromatic/aliphatic C–H vibrations
~2361 cm^{-1}	CO_2 absorption	Atmospheric CO_2 interference
~1696 cm^{-1}	C=O stretching	Carbonyl group of flavonoid structure (fisetin characteristic peak)
~1622 cm^{-1}	C=C aromatic stretching	Aromatic ring vibrations
~1570 cm^{-1}	Aromatic skeletal vibration	Confirms flavonoid nucleus
~1513–1441 cm^{-1}	C=C and C–H bending	Aromatic ring deformation
~1318–1255 cm^{-1}	C–O stretching	Phenolic C–O vibrations
~1203–1169 cm^{-1}	C–O–C stretching	Ether/glycosidic region; may indicate β-cyclodextrin interaction
~1100 cm^{-1}	C–O stretching	Strong cyclodextrin carbohydrate band
~917–882 cm^{-1}	Aromatic C–H bending	Out-of-plane bending vibrations
~518–447 cm^{-1}	Fingerprint region	Structural confirmation

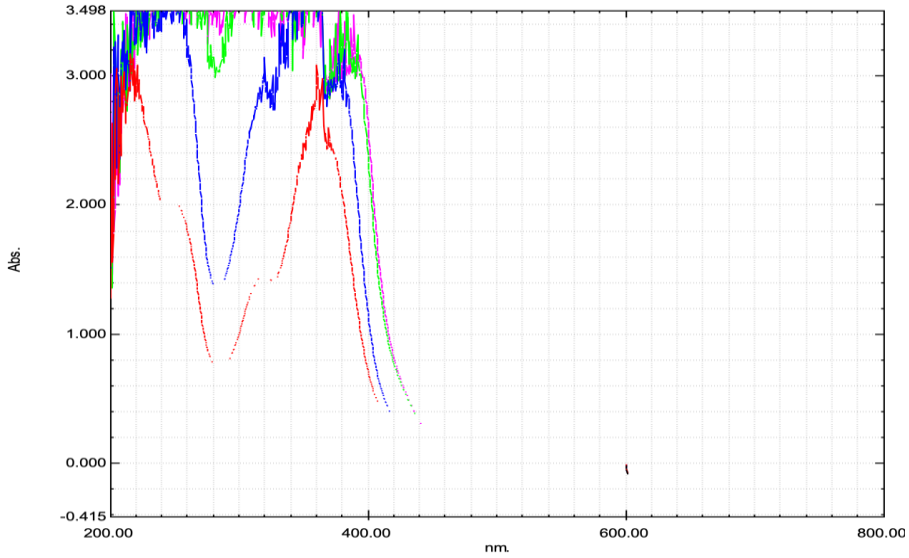
6. Calibration Curve of Fisetin

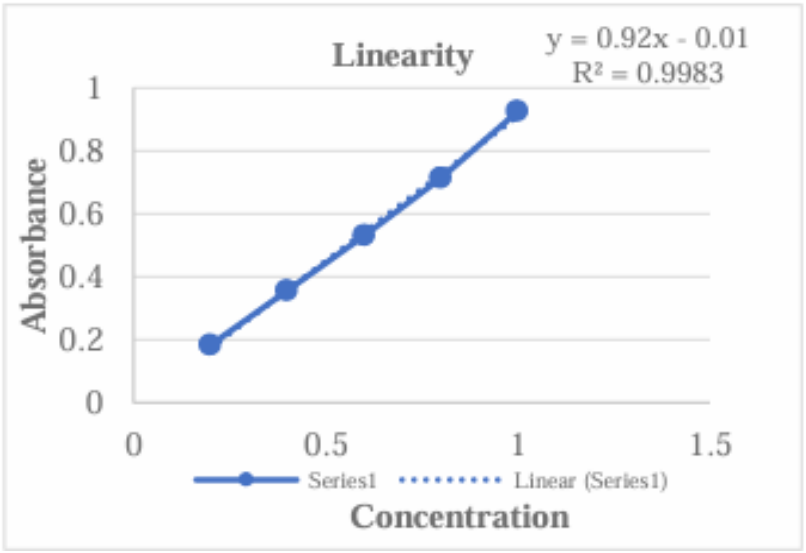
Preparation of stock solution

- Take 100mg of fisetin in 100 ml of volumetric flask
- Make volume with methanol

Preparation of working standard solution

- Take 10 ml of stock solution in 100 ml of volumetric flask
- Make volume with methanol
- Then take 1 ml of working standard solution in 100 ml of volumetric flask and make volume with methanol
- Pipette out 0.2, 0.4, 0.6, 0.8 ml dilution with Methonal in each 10 ml of volumetric flask.
- Calibration curve of Fisetin in methanol





Concentration	Absorbance
0.2	0.18
0.4	0.36
0.6	0.54
0.8	0.72
1	0.91

This curve shows the linearity as correlation coefficient is close to value 1.

7. Dissolution Test

The in-vitro drug release study of film is carried out using USP dissolution apparatus 2 (paddle method). The dissolution medium consisted of 900 ml phosphate buffer pH 7.4, maintained at 37 ± 0.5°C with continuous stirring at 50–100 rpm. Samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh buffer to maintain sink conditions. The samples were analyzed using UV–Visible spectrophotometer at 320 nm to determine the amount of drug released.

Dissolution of Pure Fisetin

S. No.	Time (Hrs.)	% Drug Release
1.	0	0
2.	1	8
3.	2	12
4.	4	18
5.	6	24
6.	8	30
7.	12	38

Dissolution of Fisetin Loaded Microsphere

S. No.	Time (Hrs.)	% Drug Release
1.	0	0
2.	1	15
3.	2	28
4.	4	45
5.	6	55
6.	8	68
7.	12	75

SUMMARY

The study successfully focused on the development of fisetin-loaded microspheres to overcome the limitations associated with the drug's poor solubility and bioavailability. The emulsion solvent evaporation method was employed using ethyl cellulose as the polymeric carrier. The prepared microspheres exhibited good physicochemical properties, including a high percentage yield and acceptable swelling behavior. Solubility studies confirmed the lipophilic nature of fisetin, justifying the use of microsphere formulation. Microscopic evaluation revealed spherical particles with uniform distribution, while FTIR studies confirmed compatibility between drug and excipients. The calibration curve showed linearity, ensuring accurate quantification of drug concentration. In vitro drug release studies demonstrated a sustained release pattern from microspheres compared to pure fisetin, indicating improved drug delivery performance. Overall, the formulation approach proved to be effective in enhancing drug release and stability, suggesting its potential application in controlled drug delivery systems.

CONCLUSION

The present study successfully formulated fisetin-loaded microspheres using the emulsion solvent evaporation technique. The developed formulation demonstrated good yield, stability, and physicochemical characteristics. FTIR analysis confirmed the compatibility of fisetin with excipients, ensuring formulation stability. The microspheres showed sustained drug release behavior compared to pure fisetin, indicating enhanced drug delivery efficiency.

The use of ethyl cellulose as a polymer effectively controlled the release of fisetin and improved its solubility profile. The formulation can be considered safe, stable, and suitable for controlled drug delivery applications. This approach provides a promising strategy to enhance the bioavailability and therapeutic efficacy of fisetin. Further studies, including in vivo evaluation, can be carried out to establish its clinical potential.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this research work.

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