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Formulation and Evaluation of Controlled Release Microsphere of Rosuvastatin and Fenofibrate

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Abstract:

The present study was aimed at the formulation and evaluation of microspheres containing Rosuvastatin and Fenofibrate for sustained and controlled drug delivery in the management of hyperlipidemia. Microspheres were prepared by the emulsion-polymerization method using polymers such as HPMC, chitosan, sodium alginate, and egg albumin. Preformulation studies including solubility analysis, melting point determination, FTIR spectroscopy, and UV spectroscopic analysis confirmed the purity, identity, and compatibility of the drugs with selected excipients. The prepared microspheres were evaluated for particle size, percentage yield, drug content, entrapment efficiency, and in-vitro dissolution behavior. Scanning Electron Microscopy revealed spherical microspheres with smooth surface morphology and uniform particle distribution. The percentage yield ranged from 70.27 ± 1.24% to 85.87 ± 1.86%, while drug content and entrapment efficiency were found to be in the range of 89.85 ± 1.43% to 96.23 ± 1.54% and 79.76 ± 1.45% to 86.34 ± 1.09%, respectively. In-vitro dissolution studies demonstrated sustained drug release for up to 12 hours, indicating effective controlled-release characteristics. Formulations containing higher polymer concentrations exhibited prolonged drug release due to enhanced matrix integrity and diffusional resistance. Among all formulations, F9 and F10 demonstrated superior performance in terms of entrapment efficiency, drug content, and sustained-release profile. The study concluded that microsphere-based delivery systems can effectively enhance drug release control, improve bioavailability, reduce dosing frequency, and potentially improve patient compliance in antihyperlipidemic therapy.

Keywords: Rosuvastatin; Fenofibrate; Microspheres; Sustained Drug Release; Emulsion Polymerization; Drug Entrapment Efficiency; Controlled Release; Hyperlipidemia; HPMC; Chitosan.

Introduction

Hyperlipidemia is one of the major contributors to cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke, which remain leading causes of morbidity and mortality worldwide. Effective management of elevated lipid levels is essential to reduce cardiovascular risk and improve patient outcomes.

Among the various lipid-lowering agents, Rosuvastatin and Fenofibrate are widely prescribed due to their proven efficacy in reducing serum cholesterol and triglyceride levels. Rosuvastatin acts by inhibiting HMG-CoA reductase, thereby decreasing cholesterol synthesis, while fenofibrate enhances lipid metabolism through activation of peroxisome proliferator-activated receptor alpha (PPAR-α). The combination therapy of these drugs provides a synergistic effect in the treatment of mixed dyslipidemia and associated cardiovascular complications.

Despite their therapeutic benefits, both drugs exhibit certain limitations related to oral drug delivery. Rosuvastatin undergoes extensive first-pass metabolism and demonstrates relatively low oral bioavailability, whereas fenofibrate possesses poor aqueous solubility, resulting in variable absorption and inconsistent therapeutic response. Conventional dosage forms often require repeated administration to maintain effective plasma drug concentrations, which may lead to poor patient compliance and increased risk of adverse effects.

Therefore, the development of an advanced drug delivery system capable of providing sustained and controlled drug release is of significant pharmaceutical interest. Microsphere-based drug delivery systems have emerged as an effective approach for improving the bioavailability and therapeutic efficacy of poorly soluble and short half-life drugs. Microspheres are free-flowing spherical particles consisting of polymers that encapsulate the drug and release it in a controlled manner over an extended period. These systems offer several advantages, including prolonged drug release, reduced dosing frequency, improved patient compliance, minimized side effects, and enhanced stability of the encapsulated drug. Controlled release from microspheres can maintain steady-state plasma drug concentrations for longer durations, thereby improving therapeutic efficiency and reducing fluctuations in drug levels.

Various polymers and encapsulation techniques such as solvent evaporation, ionic gelation, and emulsion polymerization have been extensively investigated for microsphere preparation. The selection of suitable polymers and optimization of formulation variables such as polymer concentration, stirring speed, and cross-linking conditions play a crucial role in determining microsphere characteristics including particle size, morphology, drug loading, and entrapment efficiency. Proper optimization is essential to achieve desirable release profiles and stable formulations. In the present study, an attempt was made to formulate and evaluate microspheres containing rosuvastatin and fenofibrate for controlled drug delivery. The prepared microspheres were characterized for physicochemical properties, particle size, morphology, entrapment efficiency, drug loading, and in-vitro drug release behavior. Stability and compatibility studies were also carried out to ensure formulation integrity and long-term performance. The study aimed to develop an optimized microsphere formulation capable of enhancing bioavailability, maintaining sustained drug release, reducing dosing frequency, and minimizing toxic or adverse effects associated with conventional therapy.

Materials and Methods

Equipment and Instruments

The present investigation utilized various analytical and pharmaceutical instruments for the preparation and evaluation of microspheres containing Rosuvastatin and Fenofibrate. An analytical balance (Shimadzu AUW220D) was used for accurate weighing of drug and excipients. A digital pH meter (Labindia LI-120) was employed for pH determination of formulations and buffer solutions.

Drying of microspheres and glassware was carried out using a hot air oven (Narangs Scientific Works NSW-143). Quantitative estimation of drug content and dissolution samples was performed using a UV–Visible spectrophotometer (Shimadzu UV-1800). Drug–excipient compatibility studies were conducted using an FTIR spectrophotometer (Shimadzu IRAffinity-1S).

A magnetic stirrer (REMI 2MLH) was utilized during microsphere preparation to maintain continuous stirring and uniform dispersion.

Chemicals and Reagents

Rosuvastatin and Fenofibrate were used as active pharmaceutical ingredients for antihyperlipidemic activity. Hydroxypropyl methylcellulose (HPMC) and sodium alginate were employed as sustained-release polymers and matrix-forming agents.

Sodium bicarbonate was used as a gas-generating agent, while ethanol and dichloromethane served as solvents during microsphere preparation. Sodium lauryl sulphate acted as a surfactant and n-hexane was used for washing the prepared microspheres. All chemicals and reagents used in the study were of analytical grade.

Characterization of Materials and Preformulation Studies

Identification Test of Drug API

Identification by FTIR Spectroscopy

The identity and compatibility of Rosuvastatin and Fenofibrate were confirmed using Fourier Transform Infrared (FTIR) spectroscopy. Dried potassium bromide (KBr) powder was mixed uniformly with the drug sample, compressed into pellets, and scanned to obtain characteristic absorption peaks corresponding to functional groups of the drugs.

Identification by UV Spectroscopy

For UV spectroscopic identification, 100 ppm solutions of Rosuvastatin and Fenofibrate were prepared in methanol and scanned over a wavelength range of 200–400 nm using a UV–Visible spectrophotometer. The absorption maxima (λmax) were recorded and compared with reported values.

Solubility Studies

Solubility studies were performed using the equilibrium solubility method in solvents of varying polarity. Excess amounts of Rosuvastatin and Fenofibrate were added separately to different solvents and stirred continuously for 2 hours until equilibrium was achieved. The mixtures were filtered and analyzed spectrophotometrically to determine drug solubility.

Melting Point Determination

The melting points of the drugs were determined by capillary method using Thiele's tube containing liquid paraffin. The temperature at which complete melting of the drug occurred was recorded and compared with standard values.

Preparation of Microspheres: Microspheres containing Rosuvastatin and Fenofibrate were prepared by the emulsion-polymerization method. The drug and polymer were dissolved in a solvent mixture of dichloromethane and ethanol to form the

polymeric phase. This phase was added into 10% egg albumin solution under continuous stirring to obtain a uniform dispersion.

Separately, coconut oil containing sodium lauryl sulphate was prepared as the organic phase.

The polymeric phase was added dropwise into the organic phase using a syringe needle while stirring continuously at 700 rpm for 2 hours.

Formaldehyde was then added as a cross-linking agent to stabilize the microspheres. The prepared microspheres were washed repeatedly with n-hexane, dried, and stored in a desiccator for further evaluation.

Different formulation batches (F1–F10) were prepared using varying concentrations of HPMC and chitosan while maintaining constant drug content and excipient quantities.

Evaluation of Microspheres

Particle Size Determination: Particle size analysis of the prepared microspheres was performed to ensure uniformity and optimal biological performance.

Percentage Yield:

The percentage yield of microspheres was calculated by comparing the practical weight of the recovered microspheres with the theoretical total weight of non-volatile materials used in the formulation.

Drug Content Determination

Accurately weighed microspheres were dispersed in phosphate buffer pH 7.2, shaken thoroughly, filtered, and analyzed spectrophotometrically at 321 nm to determine drug content.

Drug Entrapment Efficiency

Entrapment efficiency was evaluated by suspending microspheres in simulated gastric fluid (pH 1.2), followed by stirring, filtration, and spectrophotometric analysis at 321 nm. The percentage of entrapped drug was calculated using the standard calibration curve.

In-vitro Dissolution Studies

In-vitro drug release studies were carried out using suitable dissolution apparatus. Dissolution medium consisted of 900 mL of pH 1.2 buffer for the initial 2 hours followed by phosphate buffer pH 6.8 for up to 12 hours. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

The dissolution data obtained were fitted into various kinetic models including zero-order, first-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell, and Weibull models to determine the mechanism and kinetics of drug release from the microspheres.

Results and Discussion

Drug Evaluation and Preformulation Studies

Solubility Studies

The solubility profile of Rosuvastatin and Fenofibrate was evaluated in different solvents to determine suitable media for formulation development.

Rosuvastatin was found to be soluble in pH 1.2 buffer and sparingly soluble in water, while fenofibrate showed good solubility in pH 6.8 buffer but remained insoluble in water.

Both drugs exhibited slight solubility in ethanol. The observed solubility behavior confirmed the need for an advanced drug delivery system to enhance dissolution and oral bioavailability, particularly for fenofibrate due to its hydrophobic nature.

Table 1: Solubility Studies

Solvent	Rosuvastatin	Fenofibrate
Water	Sparingly Soluble	Insoluble
Ethanol	Slightly Soluble	Slightly Soluble
pH 6.8 buffer	Slightly Soluble	Soluble
pH 1.2 Buffer	Soluble	Slightly Soluble

Melting Point Determination

The melting points of Rosuvastatin and Fenofibrate were determined using the capillary method. Rosuvastatin showed a melting point of 179.3°C, whereas fenofibrate exhibited a melting point of 79.8°C. The observed values were in close agreement with the reported standard values, confirming the purity and identity of the drugs used in the study.

FTIR Spectroscopy

FTIR spectral analysis was performed to identify the characteristic functional groups and to evaluate drug purity.

The FTIR spectrum of Rosuvastatin showed characteristic peaks corresponding to aromatic C–H stretching, N–H bending, C=O stretching, C–N stretching, and C–Cl stretching vibrations. Similarly, the FTIR spectrum of Fenofibrate exhibited characteristic absorption peaks at 2940.06 cm^{-1} (C–H stretching), 1710.01 cm^{-1} (C=O stretching), 1519.51 cm^{-1} (aromatic C–C stretching), 1452.33 cm^{-1} (CH_2 bending), 1090.73 cm^{-1} (C–O stretching), and 710.29 cm^{-1} (C–Cl stretching). The obtained spectra were found to be consistent with standard reference spectra, confirming the identity and compatibility of the drugs.

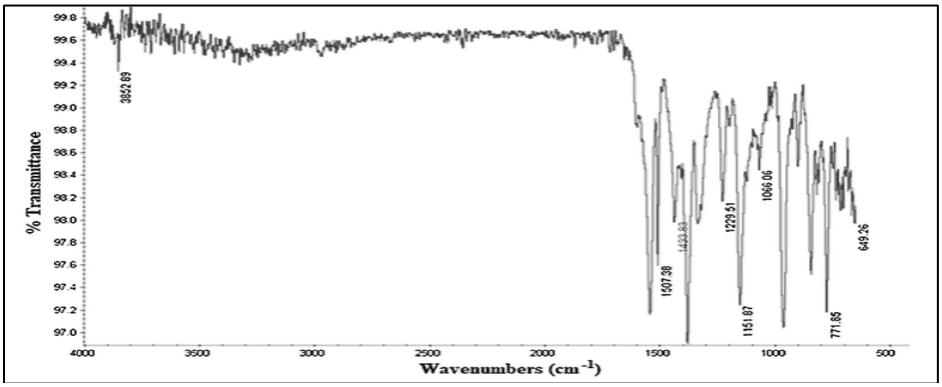

Figure 1: FTIR Spectrum of Rosuvastatin

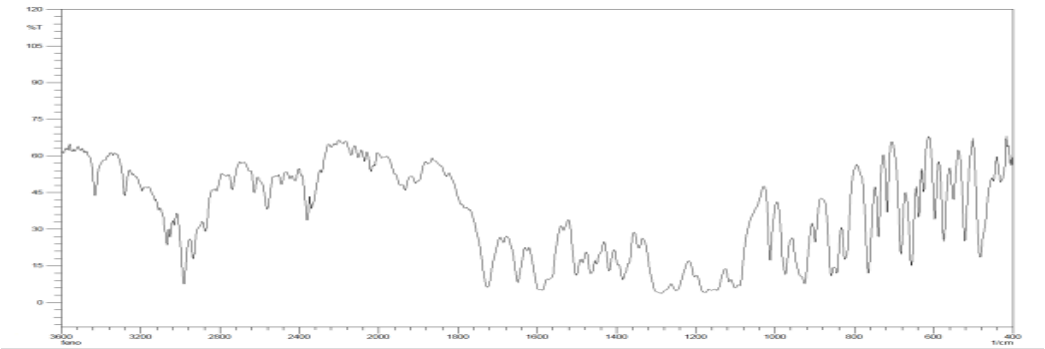

Figure 2: IR Spectra of Fenofibrate

Determination of λmax: UV spectroscopic analysis revealed that Rosuvastatin exhibited maximum absorbance at 244 nm, while Fenofibrate showed λmax at 290 nm. These wavelengths were selected for quantitative estimation of the drugs in subsequent analytical studies.

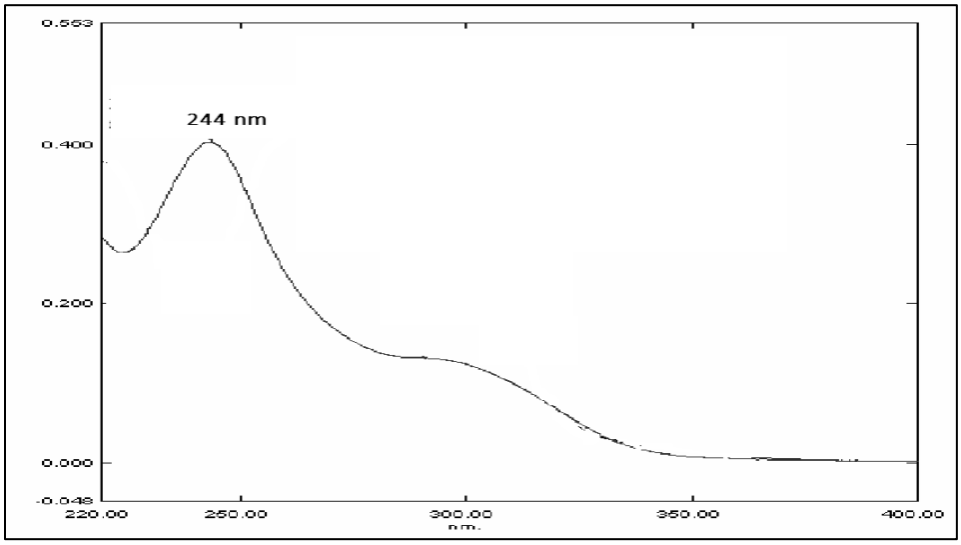

Figure 3: UV Spectra of Rosuvastatin

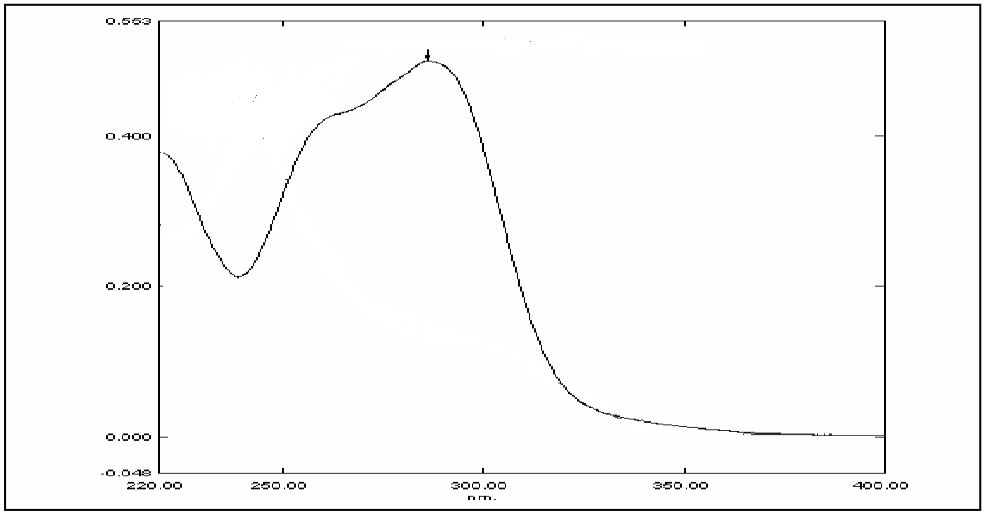

Figure 4: UV Spectra of Fenofibrate

Evaluation of Microspheres

Particle Size Analysis: Scanning Electron Microscopy (SEM) studies revealed that the prepared microspheres were spherical in shape with a relatively smooth surface morphology. Uniform particle distribution was observed, indicating effective emulsification and polymeric entrapment during microsphere preparation.

The controlled particle size contributed to improved flow properties and sustained drug release behavior.

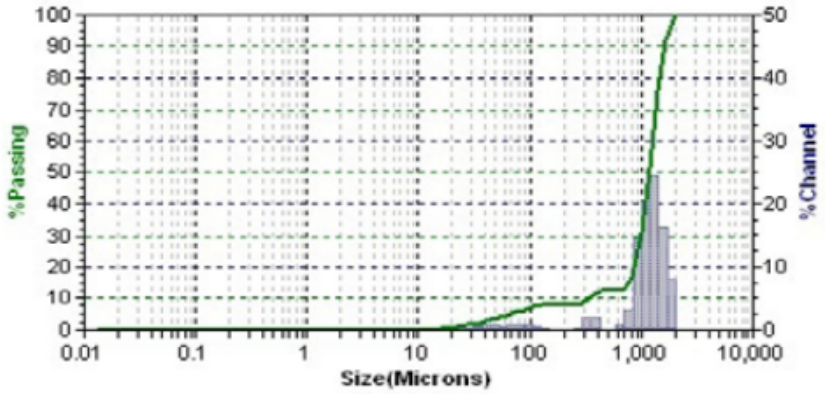

Figure 5: Particle Size Analysis

Table 2: Particle Size Analysis Data

Data	Value	Size (µm)	%Tile	% Tile	Size (µm)
MV(µm)	1.112	0.02000	0.90	10.00	0.0990
MN(µm)	20.46	0.0500	1.19	20.00	0.1620
MA(µm)	345.0	0.0900	2.51	30.00	0.768
CS	1.74E-02			40.00	10.90
SD	346.1			50.00	77.40
Mz	1.172			60.00	114.2
σ1	428.3			70.00	181.3
Skl	0.15/Σx			80.00	216.6
Kg	1.406			90.00	247.4
				95.00	270.2

Percentage Yield

The percentage yield of microspheres ranged from 70.27 ± 1.24% to 85.87 ± 1.86%. Formulations containing higher concentrations of chitosan demonstrated comparatively higher percentage yield than HPMC-based formulations.

The increase in polymer concentration enhanced the formation and recovery of microspheres by improving structural integrity during emulsification and drying processes. Among all formulations, batch F10 showed the highest percentage yield, indicating efficient formulation processing and minimal material loss. Drug content analysis demonstrated uniform distribution of Rosuvastatin and Fenofibrate within the prepared microspheres. The drug content values ranged between 89.85 ± 1.43% and 96.23 ± 1.54%. Formulations F7, F8, and F9 exhibited comparatively higher drug content, which may be attributed to better polymeric encapsulation and reduced drug loss during preparation.

The results confirmed satisfactory incorporation of both drugs into the microsphere system.

Entrapment efficiency of the microspheres ranged from 79.76 ± 1.45% to 86.34 ± 1.09%. Increased polymer concentration resulted in improved drug entrapment due to enhanced matrix formation and reduced drug diffusion into the external phase during preparation. Formulation F9 exhibited the highest entrapment efficiency, indicating effective encapsulation and strong interaction between the drug and polymeric matrix. The obtained results demonstrated that the emulsion-

polymerization technique was suitable for preparing stable microspheres with high encapsulation efficiency.

Table 3: Evaluation of Microspheres

Sr. No.	Batch	Percentage Yield	Drug Entrapment Efficiency	Drug Content
1	F1	70.27 ± 1.24	80.43 ± 1.48	90.75 ± 1.56
2	F2	72.45 ± 0.62	79.76 ± 1.45	89.85 ± 1.43
3	F3	73.84 ± 0.24	81.34 ± 0.53	91.46 ± 0.55
4	F4	75.35 ± 0.64	83.87 ± 1.23	93.27 ± 1.43
5	F5	76.24 ± 1.34	82.34 ± 1.78	92.43 ± 1.76
6	F6	80.75 ± 1.75	84.12 ± 1.65	94.87 ± 1.45
7	F7	82.35 ± 0.23	85.09 ± 1.87	95.56 ± 0.87
8	F8	83.56 ± 1.12	84.68 ± 1.34	94.98 ± 1.34
9	F9	85.76 ± 0.64	86.34 ± 1.09	96.23 ± 1.54
10	F10	85.87 ± 1.86	83.65 ± 1.31	93.78 ± 1.31

In-vitro Dissolution Studies

The in-vitro dissolution studies demonstrated sustained drug release behavior from all microsphere formulations over a period of 12 hours. Initial drug release was observed within the first 2 hours, followed by a gradual and controlled release pattern. Formulations containing higher concentrations of HPMC and chitosan exhibited slower and more prolonged drug release due to the formation of a stronger polymeric barrier that controlled drug diffusion. Among all formulations, F6 showed rapid and extensive drug release, achieving approximately 91.12% release within 6 hours, while formulations F8, F9, and F10 demonstrated more sustained release up to 12 hours. Formulation F10 exhibited the highest cumulative drug release of 92.54% at the end of 12 hours, indicating effective sustained-release characteristics.

The controlled release behavior observed in optimized formulations may contribute to maintaining therapeutic plasma concentrations for extended durations, thereby reducing dosing frequency and improving patient compliance.

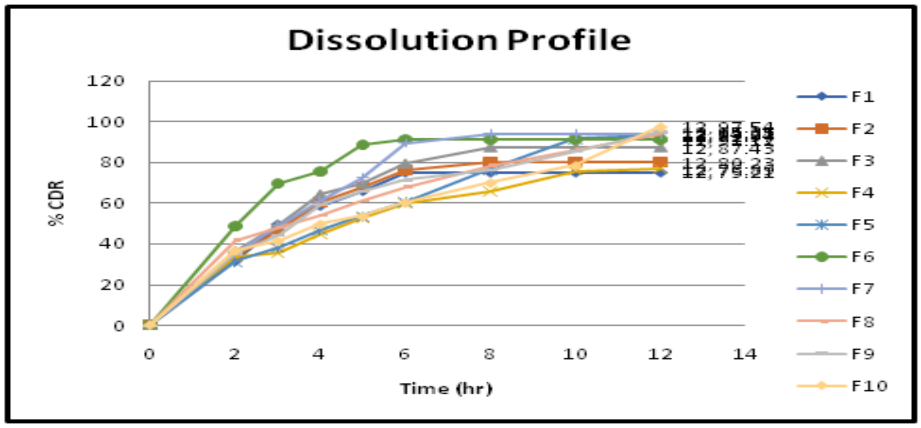

Figure 6: Dissolution Profile

The dissolution profiles suggested that polymer concentration significantly influenced drug release kinetics. Increased polymer content prolonged drug release by increasing diffusional path length and matrix integrity. Overall, the developed microspheres successfully achieved controlled release of Rosuvastatin and Fenofibrate and demonstrated potential as an effective oral sustained-release drug delivery system.

Conclusion

The present investigation successfully demonstrated the formulation and evaluation of Rosuvastatin and Fenofibrate-loaded microspheres using the emulsion-polymerization technique. Preformulation studies confirmed the purity, compatibility, and suitability of the drugs and excipients employed in the formulation.

The prepared microspheres exhibited satisfactory physicochemical properties, including good percentage yield, high drug content, efficient drug entrapment, and uniform particle morphology. The in-vitro dissolution studies confirmed sustained and controlled drug release over an extended period, indicating the effectiveness of the polymeric matrix system.

Increased polymer concentration significantly influenced entrapment efficiency and prolonged drug release by enhancing matrix integrity and diffusional path length.

Among the prepared batches, formulations F9 and F10 demonstrated optimum performance with improved drug encapsulation and sustained-release characteristics. Overall, the developed microsphere formulations showed significant potential for improving oral bioavailability, maintaining prolonged therapeutic drug concentrations, reducing dosing frequency, and minimizing adverse effects associated with conventional dosage forms.

The study suggests that microsphere-based controlled-release systems can serve as an effective and promising approach for the delivery of antihyperlipidemic drugs such as Rosuvastatin and Fenofibrate.

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