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FORMULATION, DEVELOPMENT, AND CHARACTERIZATION OF FENOFIBRATE NANOPARTICLES

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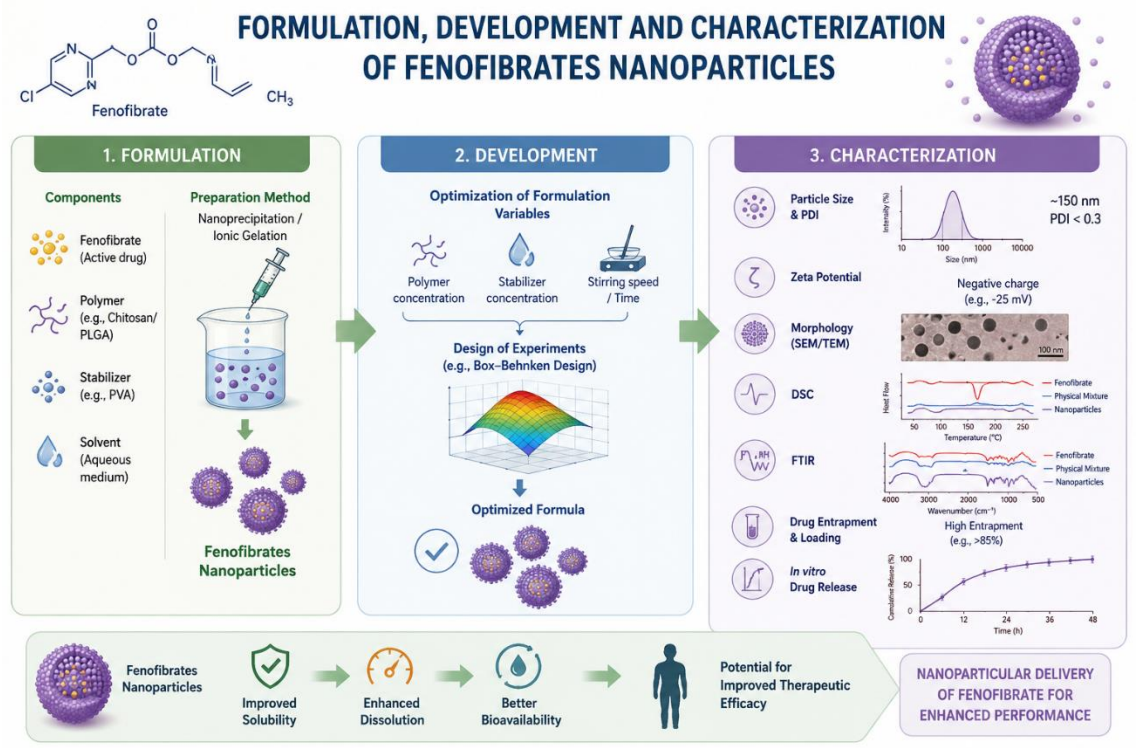
ABSTRACT

Fenofibrate is a widely used antihyperlipidemic drug indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia. However, its poor aqueous solubility and low oral bioavailability significantly limit its therapeutic effectiveness. Nanoparticle-based drug delivery systems have emerged as a promising approach to overcome these limitations by enhancing solubility, dissolution rate, and bioavailability. The present study aimed to formulate, develop, and characterize fenofibrate nanoparticles to improve its pharmaceutical performance and therapeutic efficacy.Fenofibrate nanoparticles were prepared using a suitable nanoparticle fabrication technique and optimized by varying formulation parameters such as polymer concentration, stabilizer concentration, and processing conditions. The prepared nanoparticles were evaluated indicating successful formulation. The optimized formulation exhibited high drug entrapment efficiency and satisfactory stability. Morphological studies confirmed the formation of discrete and uniformly distributed nanoparticles. In vitro drug release studies demonstrated a significantly enhanced dissolution profile compared to pure fenofibrate, suggesting improved drug availability.The developed fenofibrate nanoparticles showed favorable physicochemical characteristics and enhanced drug release properties, highlighting their potential as an effective oral drug delivery system. The reduction in particle size and increased surface area contributed to improved solubility and dissolution behavior of the drug. These findings suggest that nanoparticle-based formulations can serve as a promising strategy for enhancing the bioavailability and therapeutic performance of poorly water-soluble drugs such as fenofibrate. Further in vivo

studies are warranted to establish the clinical benefits and pharmacokinetic advantages of the developed nanoparticle formulation.

KEYWORDS: Fenofibrate, Nanoparticles, Drug Delivery System, Bioavailability Enhancement, Nanotechnology, Entrapment Efficiency, Particle Size, In Vitro Drug Release, Characterization, Lipid-Lowering Drug.

Graphical Abstract



INTRODUCTION

Fenofibrate is a lipid-lowering agent belonging to the fibrate class of drugs and is widely used in the management of hypertriglyceridemia, mixed dyslipidemia, and cardiovascular disorders associated with abnormal lipid metabolism.**[1]** It acts primarily as an agonist of peroxisome proliferator-activated receptor alpha (PPAR-α), resulting in increased lipolysis, enhanced clearance of triglyceride-rich lipoproteins, and improved lipid profiles. Despite its proven therapeutic efficacy, fenofibrate is classified as a Biopharmaceutics Classification System (BCS) Class II drug due to its poor aqueous solubility and high permeability.**[2]** The low solubility of fenofibrate leads to slow dissolution in gastrointestinal fluids, resulting in limited oral bioavailability and variable therapeutic response.Poor aqueous solubility remains one of the major challenges in pharmaceutical drug development, as a significant proportion of newly discovered drug molecules exhibit low water solubility.**[3]** Various formulation

approaches such as micronization, solid dispersions, lipid-based formulations, self-emulsifying drug delivery systems, and nanotechnology-based systems have been investigated to improve the solubility and bioavailability of poorly soluble drugs.**[4]** Among these strategies, nanoparticle technology has emerged as one of the most promising approaches due to its ability to reduce particle size to the nanometer range, thereby increasing surface area, dissolution rate, and drug absorption.Nanoparticles offer several advantages, including enhanced solubility, improved bioavailability, controlled drug release, better stability, and targeted drug delivery.**[5]** The reduction in particle size significantly improves drug dissolution according to the NoyesWhitney equation, leading to increased absorption and therapeutic effectiveness.**[6]** In recent years, nanoparticle-based drug delivery systems have gained considerable attention in pharmaceutical research because of their potential to overcome limitations associated with conventional dosage forms.The current pharmaceutical landscape emphasizes the development of advanced drug delivery systems capable of improving the therapeutic performance of poorly water-soluble drugs.**[7]** Nanotechnology-based formulations have demonstrated significant success in enhancing the pharmacokinetic and pharmacodynamic properties of various drugs. Moreover, regulatory agencies increasingly support the development of innovative nanomedicines that offer improved efficacy, safety, and patient compliance. In research in nanoparticle technology is expected to focus on the development of smart, targeted, and stimuli-responsive delivery systems integrated with advanced materials and personalized medicine approaches. Such innovations may further enhance drug bioavailability, reduce dosing frequency, and improve patient outcomes.**[8]**Therefore, the present study was undertaken to formulate, develop, and characterize fenofibrate nanoparticles with the aim of improving its solubility, dissolution behavior, and overall pharmaceutical performance.**[9]** The prepared nanoparticles were evaluated for various physicochemical characteristics, including particle size, zeta potential, drug entrapment efficiency, surface morphology, and in vitro drug release, to assess their suitability as an effective oral drug delivery system.**[10]**

MATERIALS AND METHODS

MATERIALS

Fenofibrate was obtained as a gift sample from a reputed pharmaceutical company and used as the active pharmaceutical ingredient. The polymer and stabilizer used for nanoparticle preparation were procured from standard commercial sources. HPLC-grade acetonitrile, methanol, and water were purchased from Merck Life Science, India. Analytical-grade

chemicals and reagents required for formulation development and characterization studies were obtained from recognized chemical suppliers. All solvents and reagents used in the study were of analytical reagent grade and were used without further purification. Double-distilled water was used throughout the experimental work. All materials were stored under appropriate laboratory conditions until use.

METHODOLOGY

1. Chemicals and Reagents

Fenofibrate reference standard was obtained as a gift sample from a reputed pharmaceutical company. The polymer and stabilizer used for nanoparticle preparation were procured from certified commercial suppliers. HPLC-grade acetonitrile, methanol, and water were purchased from Merck Life Science and used throughout the study. Analytical-grade chemicals and reagents required for formulation development and characterization were obtained from standard chemical suppliers. All aqueous solutions were prepared using purified water obtained from a Milli-Q water purification system. The reagents used for pH adjustment and other analytical procedures were of analytical reagent grade. All chemicals and solvents were used as received without further purification.

$w + x + y + z = 20$ (Polysorbates 20, 40, 60, 65, 80, and 85)

Functional category: Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent. Description: Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 25°C is yellow oily liquid. Solubility: soluble in ethanol, water and insoluble in mineral oil, vegetable oil.

METHODOLOGY

Characterization of Fenofibrate Organoleptic properties: Take a small quantity of sample and spread it on the white paper and examine it visually for color,odour and texture. Determination of Fenofibrate Melting point The melting point of Fenofibrate was determined by capillary tube method according to the USP. A sufficient quantity of Fenofibrate powderwas introduced into the capillary tube to give a compact column of 4-6mm in height. The tube was introduced in electrical melting pointapparatus and the temperature was raised. The melting point wasrecorded, which is the temperature at which the last solid particle ofFenofibrate in the tube passed into liquid phase. Determination of Fenofibrate Solubility Determination of solubility of drug by visual observation. Anexcess quantity of Fenofibrate was taken separately and adds in10 ml of different solutions. These solutions were shaken

wellfor few minutes. Then the solubility was observed andobservations are shown in theTable. Analytical Method Development Determination of absorption maxima: Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Procedure: For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of Methanol(1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (pH 5.5). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200 400 nm using double beam UV spectrophotometer. The absorption maxima were obtained at 290nm with a characteristic peak.

Method of Manufacture: Polysorbates are prepared from sorbitol in a three-step process. Water is initially removed from the sorbitol to form a sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is chemically added in the presence of a catalyst to yield the polysorbate. Storage: Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place. 32 EXCIPIENTS PROFILE Surface tension: 42.5 Specific gravity: 1.08 Hydroxyl value: 65–80 Moisture content: 3.0 Saponification value: 45–55 Acid value: 2.0 Flash point: 149°C HLB value: 15.0.

Preparation of Fenofibrate loadednanoparticles.

Fenofibrate loaded Nanoparticle was prepared by previously reported emulsification sonication method. Fenofibrate wasdissolved in organic solvent (10 ml, methanol). Polymers in different concentrations were dissolved in water. The organic phase was added drop wise into the polymeric solution for emulsification. Then the dispersion was sonicated (20 min) with the application of ultra-probe sonication (60 W/cm3, Hielscher, Ultra-sonics, Germany). The formulation was stirred at 1500 rpm for 6 h using a magnetic stirrer to evaporate the organic solvent. The prepared NPs were centrifuged at 15,000 rpm for 20 min at 4 °C (Remi, Mumbai, India). NPs were separated and lyophilized using cryoprotectant (Mannitol 0.2%) and stored for further evaluation.

Table no. 1 Compositionofnanoparticlesformulations.(R1toR9)

Excipients	R1	R2	R3	R4	R5	R6	R7	R8	R9
Fenofibrate	10	10	10	10	10	10	10	10	10
Sodiumalginate (%)	1	2	3	-	-	-	-	-	-
Chitosan(mg)	-	-	-	1	2	3	-	-	-
Ethylcellulose	-	-	-	-	-	-	1	2	3
Tween80(mL)	0.4	0.6	0.8	0.4	0.6	0.8	0.4	0.6	0.8
Distilledwater (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10
Methanol: AcetoneRatio	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3

Characterizationofnanoparticles:

ParticleSizes,PDI,ZetaPotential:

Themeanparticlelengthandpolydispersityindex(PDI),that'sadegreeofthe distributionofnanoparticlespopulation,wasdecidedtheusageofdynamiclight scattering (Delta NanoC, Beckman counter), andZetacapability becomes anticipated onthepremise of electrophoretic mobility underan electric poweredfield,theuse of zeta Sizer Nano ZS (Malvern Instruments, UK). Samples had been diluted with thedistilledwater before measurement and measure at a hard and fast angle of 1650c for the particle size and polydispersity index (PDI) analysis. For the Zeta ability measurement,Samples have been diluted as 1;40ratio with filtered water (v/v) before analysis. Average particle size, PDI, and zeta potential have been then measured in triplicate.

Powder X-ray Diffraction (PXRD) Studies

PXRD analysis was performed to evaluate the crystalline nature of fenofibrate and the prepared nanoparticle formulation. This technique helps in identifying changes in crystallinity, crystal lattice arrangement, and the formation of new solid phases. Differences in diffraction peak positions and intensities indicate possible modifications in the physical state of the drug after nanoparticle preparation. PXRD is also useful for structural characterization and studying drug–excipient interactions.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was carried out to investigate the compatibility between fenofibrate and the excipients used in the formulation. The spectra of pure drug and optimized nanoparticles were compared to identify any possible chemical interactions. Characteristic functional group peaks were analyzed to confirm the integrity of the drug molecule. FTIR studies also help in verifying the successful incorporation of the drug into the nanoparticle system.

In Vitro Drug Release Studies

In vitro drug release studies were conducted to evaluate the release behavior of fenofibrate from the nanoparticle formulation. The study provides information regarding the rate and extent of drug release under simulated physiological conditions. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically for drug content. The release profile helps in assessing the potential of nanoparticles for sustained and improved drug delivery.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed to study the thermal behavior of fenofibrate and the optimized nanoparticle formulation. The technique helps in detecting possible interactions between the drug and excipients by analyzing changes in melting point and thermal transitions. Variations in thermograms may indicate changes in crystallinity or successful drug encapsulation. DSC is an important tool for evaluating the physical stability of pharmaceutical formulations.

Scanning Electron Microscopy (SEM) Studies

SEM analysis was carried out to examine the surface morphology and shape of the prepared nanoparticles. The technique provides high-resolution images that reveal particle size, surface characteristics, and uniformity of the formulation. Samples were coated with a thin conductive layer before imaging to obtain clear micrographs. SEM studies help in confirming the successful formation of nanoparticles and assessing their morphological properties.

RESULTS AND DISCUSSION

Organolepticproperties

Table8.1:Organolepticproperties

SNO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odourless
4	Meltingpoint	80to81°C

Solubilitystudies

Table8.2:Solubilitystudiesofdrugindifferentsolvents

SNO.	Solvents	SolubilityofFenofibrate
1	Ethanol	Freelysoluble
2	Methanol	Sparinglysoluble
3	DMSO	Freelysoluble
4	Acetonitrile	Soluble
5	PhosphatebufferpH-5.5	Freelysoluble

CALIBRATIONPLOTOFFENOFIBRATEPHOSPHATEBUFFEROFpH-5.5:

A standard graph of Fenofibrate in phosphate buffer of pH-5.5 was plotted using Absorbance and concentration as shown in Table and Fig. Equation for linearity curve and R^2 were calculated as Y=0.011X+0.011 and R^2=0.997. Fenofibrate showed maximum absorbancein phosphate buffer (pH 5.5) at 290 nm. The solution obeyed Beer-Lambert's law for concentration range of 10 to 50µg/mL with regression coefficient of 0.997. Standard curve of prepared Fenofibrate in phosphate buffer pH 5.5 is shown below.

Table8.3:CalibrationcurveofFenofibrateinphosphatebufferpH5.5

Concentration(µg/mL)	Absorbance
0	0
10	0.145
20	0.234
30	0.351
40	0.468
50	0.582

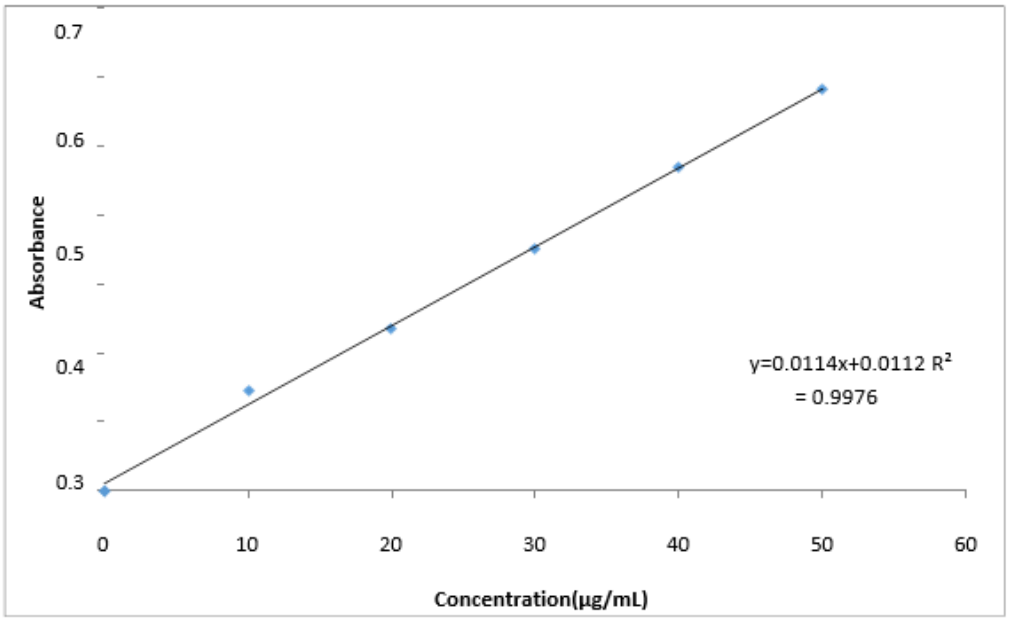


Fig8.1:CalibrationcurveofFenofibrateinphosphatebufferpH5.5Characterizationofnanoparticles.

Table8.4:Percentageyield,DrugContent,Entrapment Efficiencyofallnanoparticlesformulations.

FORMULATION	Percentageyield	DrugContent	Entrapment Efficiency
F1	82.28	90.14	61.14
F2	89.34	93.04	71.25

F3	92.15	94.45	88.01
F4	91.54	95.03	51.82
F5	93.54	96.32	60.82
F6	**95.81**	**97.59**	**75.14**
F7	86.09	92.64	60.19
F8	90.47	94.82	69.25
F9	93.78	95.61	72.10

Percentage yield of formulations F1 to F9 by varying drug to polymer was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for F6 formulation.

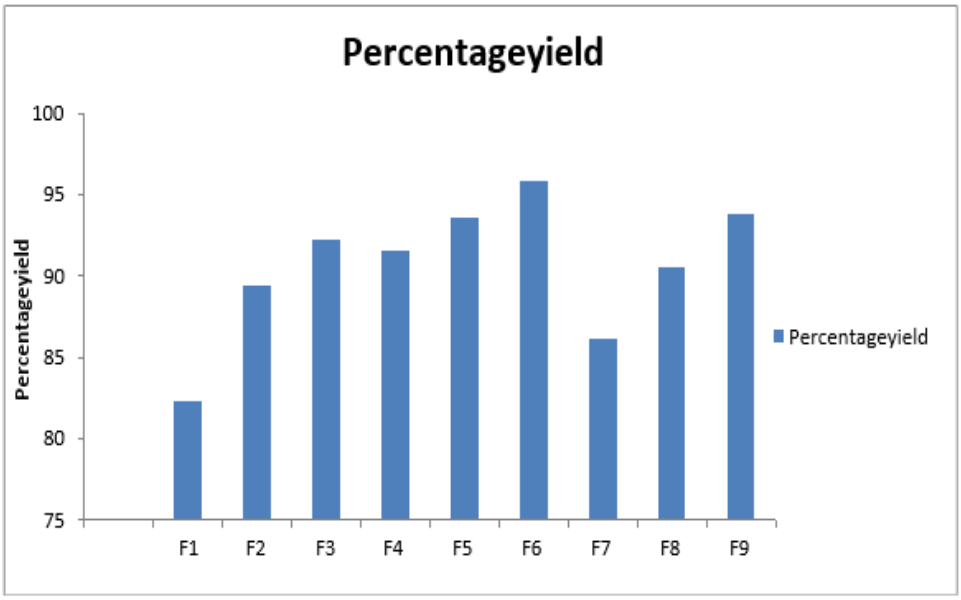


Fig8.2:Percentageyieldofallnanoparticles

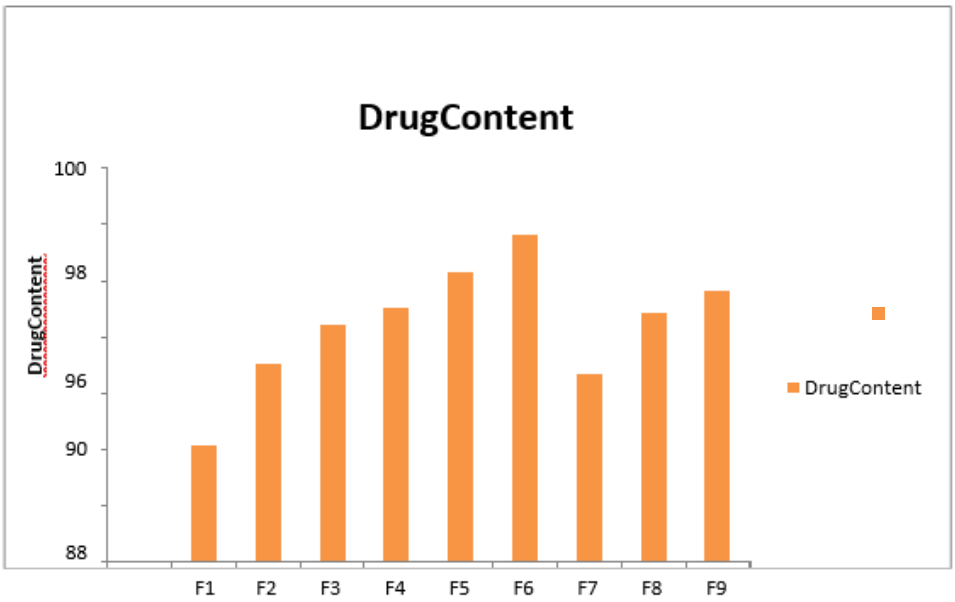


Fig8.3:DrugContentyieldofallnanoparticles

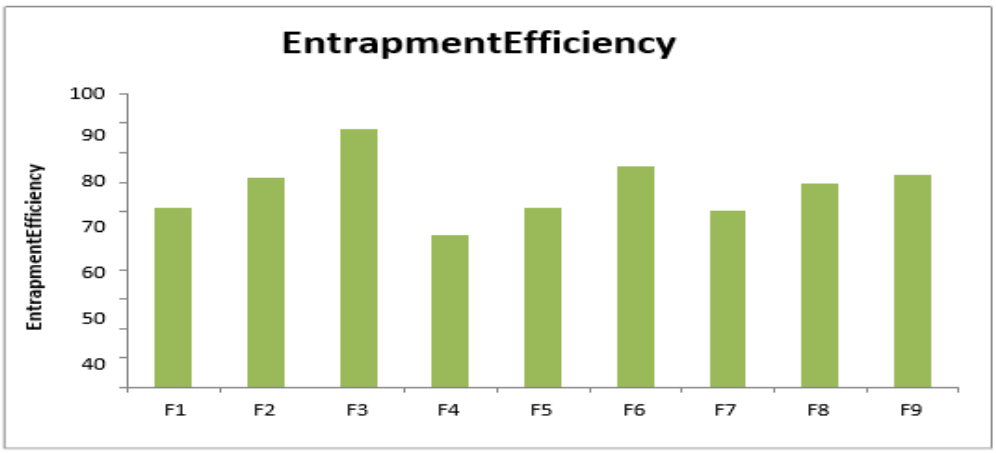


Fig8.4:EntrapmentEfficiencyofallnanoparticles

Table8.5:ParticleSizes,PDIandZetaPotentialofallnanoparticlesformulations

FORMULATION	ParticleSize(nm)	PDI	ZetaPotential (mV)
F1	175.9	0.095	-25.3
F2	162.2	0.092	-26.4
F3	156.2	0.162	-27.6
F4	168.5	0.185	-25.9
F5	151.9	0.109	-28.4
F6	**140.5**	**0.090**	**-29.5**
F7	173.9	0.159	-28.5
F8	152.2	0.132	-25.8
F9	148.3	0.123	-25.4

The particle size of the all formulations was observed in the range of 140.5 to 173.9. The less particle size, PDI observed in the F6 formulation i.e., 0.090 nm respectively. The Zeta potential range from-25.3 mV to -29.5mV to allthe formulations.The negative charge on the surface of the Nanoparticle is believed to facilitate uptake fromthe intestine bythe Payers patch, leading to the lymphatic circulation, also it is believed to prevent entangling of the nanoparticles in the negatively charged mucous owing to the repulsion of like charges.

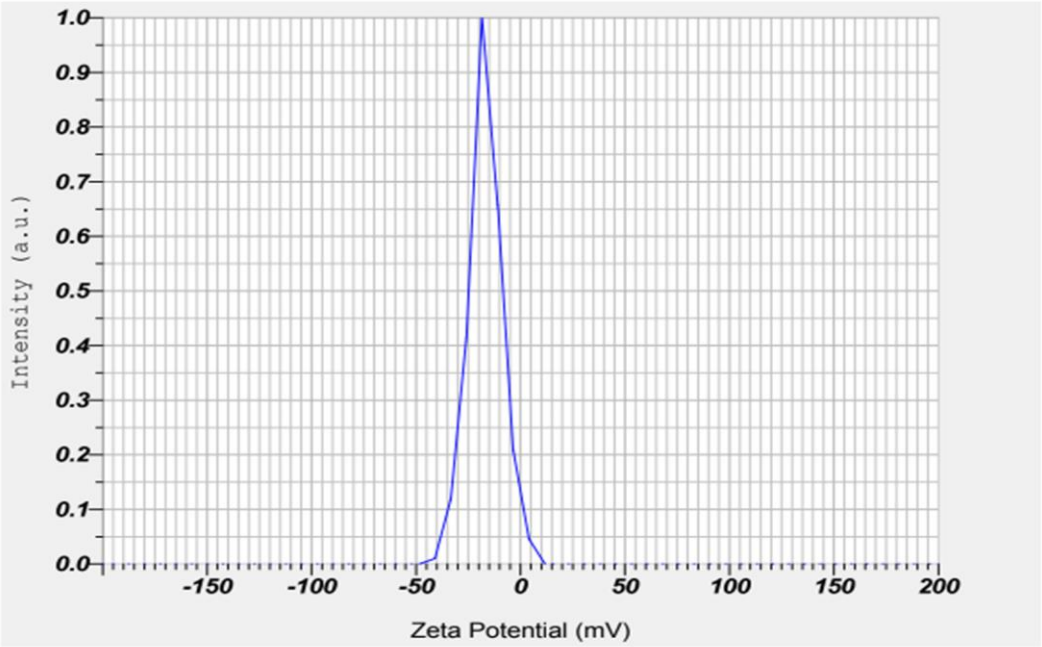


Fig8.5:ZetapotentialofF6Formulation

Table6:*Invitro*dissolutionstudiesofF1-F9nanoparticlesformulationsinpercentage

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.52	8.39	7.19	10.96	14.62	10.58	13.72	10.41	12.38
2	17.37	16.17	19.72	14.83	19.68	15.64	18.14	16.34	18.29
4	27.48	25.35	23.93	21.78	25.64	27.11	25.76	21.92	23.71
6	42.26	36.17	29.54	27.41	31.48	38.97	35.10	28.76	32.92
8	54.18	48.86	35.41	35.79	36.95	45.65	46.28	33.63	38.49
10	58.71	56.61	39.76	41.86	48.72	52.74	55.19	45.21	46.58
12	66.33	69.14	56.19	67.31	69.39	64.22	64.98	49.34	58.26
18	75.85	75.59	64.72	73.22	78.14	75.94	69.75	57.27	69.15
24	83.95	83.61	67.29	81.89	87.58	90.19	74.15	68.34	76.87
48	86.78	85.34	72.34	92.15	94.11	**98.76**	89.37	83.27	80.62

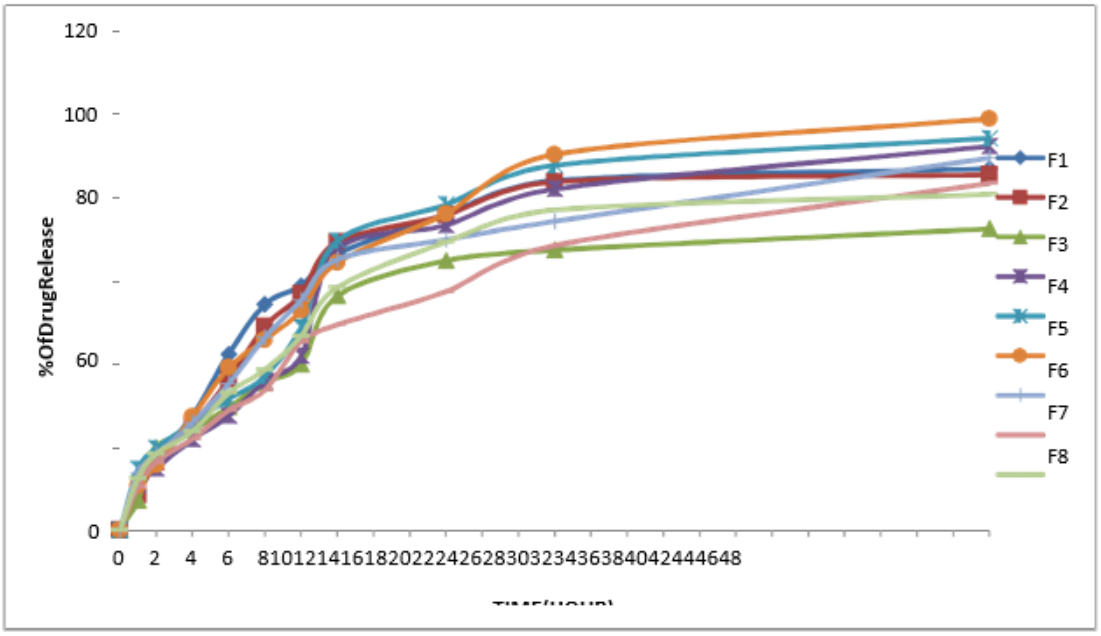


Fig9:*Invitro*dissolutionstudiesofF1-F9nanoparticles formulations inpercentage

Invitro drug release study of the selected nanoparticles (F1, F2, F3, F4, F5, F6, F7, F8 and F9) was carried out. The nanoparticles exhibited 48 hours sustained release pattern. 15.64 of the incorporated amounts of drugs were found to be released during the first 2 hours, followed by a slowed release of 98.76 % ofthe drug upto 48 hours. The Fenofibrate - loaded nanoparticles F6 showed a better release profile of98.76% by 48 hours. The prolonged release at 48 hours can be attributed to slow diffusion of drug frompolymer matrix. The results of *invitro* drug release are depicted in above Table.

CONCLUSION

The present study successfully developed and evaluated fenofibrate-loaded nanoparticles with the objective of achieving sustained drug release and improving the therapeutic performance of fenofibrate. The prepared formulations were characterized using various analytical techniques, including PXRD, FTIR, DSC, SEM, and in vitro drug release studies. The characterization results confirmed the successful incorporation of the drug into the nanoparticle system without any significant drug–excipient interaction. SEM analysis revealed the formation of nanoparticles with suitable morphology, while PXRD and DSC studies indicated changes in the crystalline nature of the drug, suggesting effective encapsulation within the polymeric matrix.

The in vitro drug release studies demonstrated that all formulations exhibited a controlled and sustained release profile over a period of 48 hours. An initial release of 15.64% drug was

observed within the first 2 hours, followed by a gradual release pattern. Among all formulations, F6 was identified as the optimized formulation, showing the highest cumulative drug release of 98.76% at the end of 48 hours. The sustained release behavior was attributed to the slow diffusion of the drug through the polymer matrix. Overall, the results suggest that formulation F6 has promising potential as an effective nanoparticulate drug delivery system for enhancing the bioavailability and therapeutic efficacy of fenofibrate while reducing dosing frequency and improving patient compliance.

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Conflict of Interest

The authors announce that there is no disagreement of interest associated with this research work.

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