

# Formulation and Evaluation of Fenofibrate-loaded Nanoparticles by Precipitation Method

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Shelake, *et al.*: Fenofibrate-loaded Nanoparticles by Precipitation Method

Nanoparticles have applications in the formulation of poorly water soluble drugs to improve their bioavailability. Preparation and evaluation fenofibrate-loaded nanoparticles by precipitation method to enhance solubility and bioavailability was the primary aim of the present investigation. Nano particles of fenofibrate, a BCS class II drug, were prepared by precipitation technique and characterized using Fourier-transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy, zeta potential and drug release studies *in vitro*. Data from the differential scanning calorimetry, powder X-ray diffractometry and Fourier-transform infrared spectroscopy showed no interaction between drug and the polymers. Scanning electron microscopy images indicated that nanoparticles were spherical in shape. Water solubility of drug-loaded nanoparticles was increased as compared to the pure drug and showed improved dissolution profile, which indicated that nanoprecipitation was simple and precise. This laboratory scale method as well as this approach could be employed for solubility and bioavailability improvement of BCS class II drugs.

**Key words:** Fenofibrate, BCS class II drug, antilipidemic, nanoprecipitation, bioavailability

The major nanoparticulate drug delivery system is liposomes and polymeric nanoparticles have particular advantage for site-specific drug delivery and to enhance the dissolution rate along with bioavailability of poorly water soluble drugs<sup>[1]</sup>. Formation of drug-loaded nanoparticles is actually a very promising approach. Particle size reduction to the nanometre range can be achieved using various techniques and these techniques have been extensively described<sup>[2]</sup>. Poor solubility and low dissolution rate of Biopharmaceutical Classification System (BCS) class II drugs in the aqueous gastrointestinal fluids often causes insufficient bioavailability and this can only be enhanced by increasing the solubility and dissolution rate by using various novel techniques<sup>[3]</sup>. Some of the techniques employed to improve drug dissolution rate are solid dispersion, inclusion complex formation, microparticles and nanoparticles.

Nanoparticles are colloidal particles ranging from 10 to 1000 nm, in which the active principles (drug or biologically active material) are dissolved, entrapped<sup>[4]</sup>. And these are of different types include, nanospheres, nanocapsules, dendrimers, solid-lipid

nanoparticle, polymeric micelles and liposomes. With the development in nanotechnology, it is now possible to produce drug nanoparticles that can be utilized in a variety of innovative ways. New drug delivery pathways can now be used to increase drug efficacy and reduce side effects<sup>[5]</sup>. Solid-lipid nanoparticles are at the rapidly developing field of nanotechnology with several potential applications in the clinical medicine and research. Nanoparticles are receiving considerable attention for the delivery of therapeutic drugs. Depending on the physicochemical characteristics of a drug, it is now possible to choose the best method of preparation with the best polymer to achieve an efficient entrapment of the drug<sup>[6]</sup>. Different methods for the preparation of nanoparticles are available, which include, solvent evaporation, nanoprecipitation, emulsification/solvent diffusion, salting out, dialysis, supercritical fluid technology and rapid expansion of

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supercritical solution, rapid expansion of supercritical solution into liquid solvent.

The Nanoprecipitation technique (or solvent displacement method) is a straightforward technique, rapid and easy to perform. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in an aqueous medium in presence or absence of a surfactant. It requires two solvents that are miscible with water. Ideally, both, the polymer and the drug should be soluble in one solvent and insoluble in another (non-solvent). Nanoprecipitation occurs by a rapid desolvation of the polymer when the polymer solution is added to the non-solvent (aqueous solution). Indeed, as soon as the polymer-containing organic solvent has diffused into the aqueous medium, the polymer precipitates, involving immediate drug entrapment. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension. This technique is most suitable for hydrophobic compounds soluble in ethanol or acetone, but has very limited solubility in water.

Fenofibrate is an antilipidemic agent, which reduces both cholesterol and triglycerides in the blood. It is used alone or along with statins in the treatment of hypercholesterolemia and hypertriglyceridemia<sup>[7]</sup>. Present work deals with the preparation and evaluation of fenofibrate-loaded nanoparticles by precipitation method.

## MATERIALS AND METHODS

Fenofibrate was received as a gift sample from Smruthi Organics Pvt. Ltd. (Solapur, India), Eudragit L-100 was purchased from Research Lab Chemical Centre, (Mumbai, India), poly vinyl alcohol, methanol and acetone were purchased from Molychem, (Mumbai, India). All other materials or chemicals used were of analytical grade.

### Preformulation study:

Preformulation is the first step in rationale development of any pharmaceutical dosage form of a new drug. Preformulation study focuses on those physicochemical properties of the new compound that can affect drug performance and development of an efficacious dosage form. These preformulation investigations confirm that there are no significant barriers to the compounds development. Melting point of fenofibrate was determined by open capillary tube method.

Drug excipients compatibility study was carried out by Fourier-transform infrared spectroscopy (FTIR, Agilent Technologies, carry 630 FTIR). The sample was analysed in the region of 4000 and 400  $\text{cm}^{-1}$ . The initial spectrum of drug and polymer mixture was taken then the same mixture of drug and polymer were kept in a stability chamber at 40° and 75 % relative humidity for 3 mo. After three months, sample mixtures were analysed by FTIR spectroscopy. The compatibility study was done by comparing initial spectra and the spectra of samples after 3 mo.

### Method of preparation:

The nanoparticles of fenofibrate were prepared by nanoprecipitation technique using the different polymer concentrations by applying a 3<sup>3</sup> factorial design as given in Table 1. Eudragit L100 was dissolved in methanol and drug in acetone separately. These two solutions were mixed and added drop-wise under stirring at 700 rpm for 120 min in aqueous solution with poly vinyl alcohol as a surfactant. After complete removal of organic solvent, it was centrifuged at 13 000 rpm and settled nanoparticles were collected and dried at 40° for 1 h<sup>[8]</sup>.

### Characterization of nanoparticles:

Organoleptic properties of the nanoparticles like colour, odour and physical appearance were observed visually and recorded. Practical yield was calculated using the Eqn.,  $\text{PY} (\%) = \frac{\text{amount of product obtained}}{\text{amount of total solid used (polymer+drug)}} \times 100$ .

### Percent drug loading and entrapment efficiency (EE):

Weighed samples of drug-loaded nanoparticles (10 mg) were dissolved in 10 ml of dichloromethane under sonication for 1 h. The samples were filtered through a membrane filter and analysed spectrophotometrically at 248 nm using a UV/Vis spectrophotometer (Shimadzu 1800). The percent drug loading and EE were determined using the below Eqns. All analyses were carried out in triplicate<sup>[9]</sup>.  $\% \text{ drug loading} = \frac{\text{mass of drug in nanoparticles}}{\text{mass of nanoparticles recovered}} \times 100$ ;  $\% \text{ EE} = \frac{\text{mass of drug in nanoparticles}}{\text{mass of drug used in preparation}} \times 100$ .

### Particle size analysis:

Determination of mean average particle size of fenofibrate nanoparticles was carried out by using Malvern instrument ver. 6.12. The analysis was performed by adding 0.3 ml sample into the viewing

**TABLE 1: EXPERIMENTAL DESIGN FOR PREPARATION OF NANOPARTICLES**

Formulation code	Independent variables		
	X1 (Drug:polymer)	X2 (Conc. of surfactant)	X3 (Ratio of organic solvent)
F1	1:4	0.5 %	1:3
F2	1:5	0.5 %	1:3
F3	1:6	0.5 %	1:3
F4	1:4	1.0 %	1:3
F5	1:5	1.0 %	1:3
F6	1:6	1.0 %	1:3
F7	1:4	1.5 %	1:3
F8	1:5	1.5 %	1:3
F9	1:6	1.5 %	1:3
F10	1:4	0.5 %	1:4
F11	1:5	0.5 %	1:4
F12	1:6	0.5 %	1:4
F13	1:4	1.0 %	1:4
F14	1:5	1.0 %	1:4
F15	1:6	1.0 %	1:4
F16	1:4	1.5 %	1:4
F17	1:5	1.5 %	1:4
F18	1:6	1.5 %	1:4
F19	1:4	0.5 %	1:5
F20	1:5	0.5 %	1:5
F21	1:6	0.5 %	1:5
F22	1:4	1.0 %	1:5
F23	1:5	1.0 %	1:5
F24	1:6	1.0 %	1:5
F25	1:4	1.5 %	1:5
F26	1:5	1.5 %	1:5
F27	1:6	1.5 %	1:5

unit dynamic light scattering is used to measure particle size and molecule size. The particle size analysis was performed at a scattering angle of 90° at room temperature. The diameter was averaged from three parallel measurements and expressed as mean±standard deviation. This technique measures the diffusion of particles moving under Brownian motion, and converts it to size and a size distribution<sup>[10]</sup>.

#### Zeta potential measurement:

The analysis was performed by using the Malvern Zetasizer ver. 6.12 (Malvern instrument, UK) the electrophoretic mobility was converted to the zeta potential. To determine the zeta potential, nanoparticle samples were diluted with KCl (0.1 mM) and placed in electrophoretic cell where an electrical field of 15.2 V/cm was applied. All measurement was performed in triplicate<sup>[11]</sup>.

#### Solubility determination:

Solubility of pure drug and all batches of nanoparticles in distilled water were obtained by adding an excess amount of the pure drug and nanoparticles in 10 ml of distilled water in conical flask to saturated solution. This conical flask was kept on orbital shaker for 24 h to ensure saturation. After attaining the equilibrium solubility, clear supernatant was filtered, appropriately diluted and analysed spectrophotometrically by UV/Vis spectrophotometer at 248 nm<sup>[12]</sup>.

#### Scanning electron microscopy (SEM):

Nanoparticles were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom) and the surface topography was analysed with a Cambridge Stereoscan S120 SEM (Cambridge, United Kingdom) operated at an acceleration voltage of 10 kV.

#### Powder X-ray diffraction analysis (PXRD):

PXRD of pure drug and optimized batch of nanoparticles were analysed by Philips PW 1729 X-ray diffractometer. Samples were irradiated with monochromatized Cu K $\alpha$ -radiations (1.542 Å) and analysed between 2-60° (2 $\theta$ ). The voltage and current used were 30 kV and 30 mA, respectively. The range was 5×10<sup>3</sup> cycles/s and the chart speed was kept at 100 mm/2 $\theta$ .

#### Differential scanning calorimeter (DSC) analysis:

Thermal properties of pure drug and optimized batch of nanoparticles were analysed by DSC (TA Instruments, USA, model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10 mg) was heated in a hermetically sealed aluminium pans. Heat runs for each sample were set from 0 to 300° at a heating rate of 10°/min.

#### In vitro drug release studies:

Nanoparticle samples were placed in dialysis bags, which were sealed and placed in dissolution medium (phosphate buffer pH 6.8 with 1 % sodium lauryl sulphate). Drug release study was carried out employing the USP dissolution test apparatus, type II at 37±0.5° and 100 rpm for 2 h. At each time interval 5 ml of sample was collected and replaced with fresh buffers. The collected samples were filtered by Whatman filter

paper 41 and analysed spectrophotometrically after the appropriate dilutions<sup>[13]</sup>.

### Factorial design/statistical analysis:

Experimental design with coded level of variables and their actual values are illustrated as the effects of the different concentrations of drug and polymer ratio (X1), concentration of surfactant (X2) and ratio of organic solvents (X3) on the responses such as practical yield (Y1), EE (Y2) and particle size (Y3).

## RESULTS AND DISCUSSION

After visual observation, the sample of fenofibrate was found to be a white and crystalline powder. The reported melting point of fenofibrate is in the range of 80 to 82° and the observed melting point was 81°, which confirmed purity of the drug. The FTIR spectra of the drug and drug with excipients were shown in fig. 1. The initial FTIR spectrum of the drug polymer mixture (1:1) showed the presence of similar functional groups as O-H stretching, C=O of COOH stretching, C=O conjugated with COOH stretching, single bond stretching of alcoholic and acidic group at 2941, 1721, 1669, 1397 cm<sup>-1</sup>, respectively, confirmed the compatibility of drug with the excipients. After 3 mo, FTIR spectra of the drug polymer mixture showed same fundamental peaks at same peak position, indicated that there is no any incompatibility between

drug and polymers. The nanoparticles were found to be white, odourless and amorphous powder.

Practical yield, drug loading and EE were given in Table 2. Practical yield of the prepared nanoparticles was in the range of 49.00±0.70 to 68.57±1.00 %. The yield of nanoparticles decreased with increasing the concentration of drug and polymer ratio, which might be due to generation of stickiness by polymer Eudragit L-100. It was found that with increasing the amount of polymer, the actual drug loading and EE increased. The EE was found to be in the range from 59.29±1.29 to 92.43±1.44 %. The drug loading of nanoparticles was found to be in the range of 22.00±1.31 to 26.95±1.24 %. It was observed that the drug content and encapsulation efficiency depends on the concentration of polymer, solvent ratio and stirring rate. On the basis of high yield, actual drug content and encapsulation efficiency batch F6 was observed as optimized batch for the preparation of nanoparticles<sup>[14,15]</sup>.

The average particle size of nanoparticles was listed in Table 3. Average particle size of nanoparticles was found to be 91±0.59 to 128±0.47 nm. The zeta potential is defined as the electrical potential between the medium and the layer of the fluid attached to the dispersed particles<sup>[16]</sup>. Zeta potential is a measure of the magnitude of the electrostatic or charge repulsion or attraction between particles and is one of the

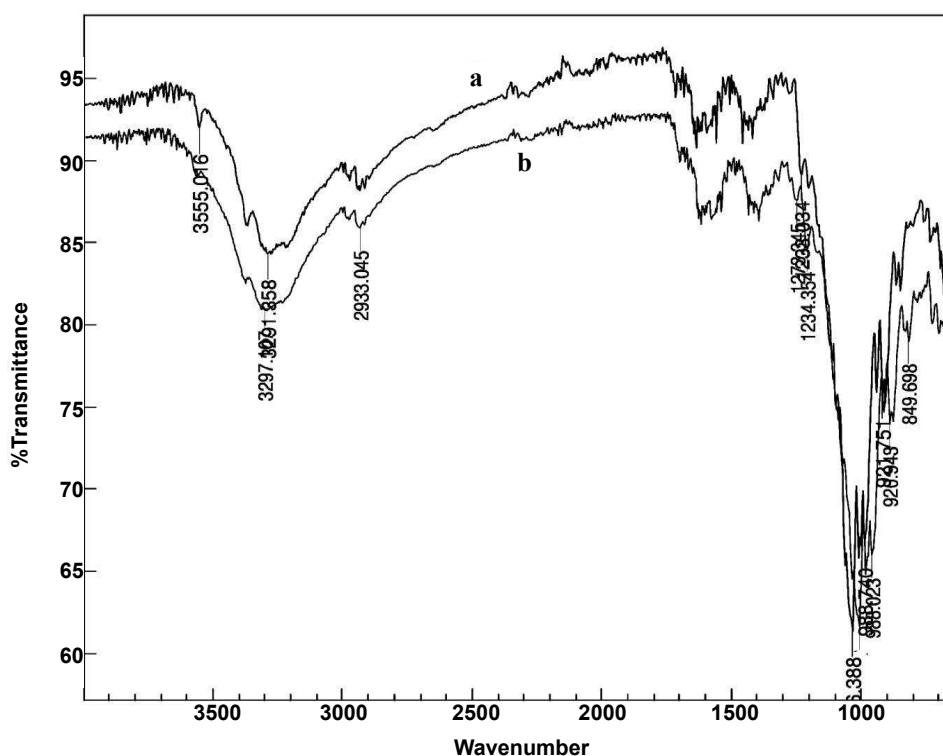


Fig. 1: FTIR spectrum of fenofibrate (a) and optimized batch F6 (b)

fundamental parameters known to affect stability. Zeta potential of prepared nanoparticles was found in range between  $0.663\pm 0.34$  to  $0.865\pm 0.37$  mV. It was found that higher the zeta potential less will be the particle

aggregation, due to electric repulsion and hence more will be the stability of nanoparticles. The zeta potential value of batch F6 was  $0.791\pm 0.32$  mV. It was observed that positive charge appears on the surface

**TABLE 2: PRACTICAL YIELD, DRUG LOADING AND ENTRAPMENT EFFICIENCY OF NANOPARTICLES**

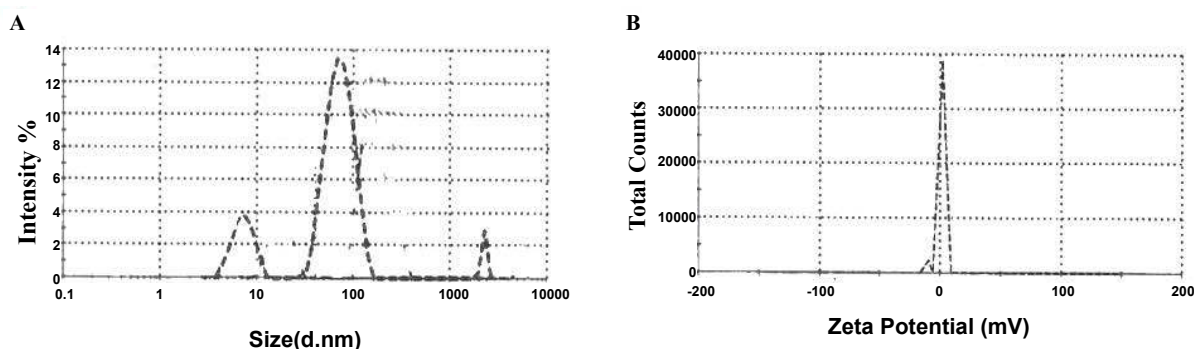
Batch code	Practical yield (%)	Drug loading (%)	Entrapment efficiency (%)	Batch code	Practical yield (%)	Drug loading (%)	Entrapment efficiency (%)
F1	49.00±0.80	25.89±1.2	63.45±1.22	F15	65.00±0.87	25.80±1.34	83.85±1.27
F2	61.66±1.02	26.19±1.2	80.77±1.45	F16	54.00±1.00	24.50±1.44	66.15±1.28
F3	65.71±1.60	26.38±1.1	86.73±1.38	F17	59.16±0.95	25.38±1.28	75.13±1.29
F4	59.00±0.90	25.89±1.3	76.40±1.52	F18	63.57±0.91	25.89±1.29	82.32±1.22
F5	65.00±1.03	26.29±1.3	85.47±1.25	F19	54.00±1.05	25.12±1.19	65.88±1.26
F6	68.57±1.06	26.95±1.2	92.43±1.44	F20	59.16±0.88	25.59±1.24	75.72±1.28
F7	57.00±1.27	25.68±1.3	73.24±1.41	F21	62.14±1.00	26.29±1.28	81.71±1.25
F8	60.83±0.70	26.08±1.2	79.35±1.51	F22	54.00±1.16	25.50±1.25	68.85±1.26
F9	65.00±1.00	26.49±1.2	86.12±1.22	F23	57.50±1.05	25.89±1.27	74.46±1.24
F10	55.00±1.08	25.09±1.2	69.02±1.20	F24	61.42±0.73	26.48±1.29	81.38±1.28
F11	60.00±0.55	25.70±1.1	77.10±1.21	F25	53.00±0.95	25.39±1.31	67.31±1.29
F12	64.28±0.67	26.19±1.2	84.20±1.31	F26	58.33±0.99	25.99±1.27	75.82±1.24
F13	54.00±1.95	24.79±1.2	66.96±1.30	F27	60.71±1.05	26.38±1.25	80.13±1.26
F14	60.83±0.94	25.18±1.3	76.64±1.28				

Each value is average of three separate determinations ±SD

**TABLE 3: MEAN PARTICLE SIZE, AVERAGE ZETA POTENTIAL AND SOLUBILITY OF NANOPARTICLES**

Batch code	Size (nm)	Average zeta potential (mV)	Solubility (mg/ml)	Batch code	Size (nm)	Average zeta potential (mV)	Solubility (mg/ml)
F1	96±0.64	0.672±0.24	2.010±0.04	F15	112±0.66	0.865±0.37	2.140±0.04
F2	104±0.44	0.681±0.28	2.145±0.06	F16	97±0.40	0.660±0.38	1.820±0.02
F3	106±0.71	0.710±0.31	2.120±0.01	F17	107±0.63	0.672±0.37	1.970±0.04
F4	109±0.61	0.669±0.31	2.140±0.03	F18	89±0.71	0.678±0.32	1.830±0.01
F5	97±1.02	0.778±0.33	2.170±0.07	F19	103±0.78	0.663±0.34	1.970±0.061
F6	91±0.59	0.791±0.32	2.190±0.08	F20	109±0.83	0.673±0.35	1.830±0.05
F7	96±0.42	0.651±0.27	2.019±0.01	F21	118±0.80	0.691±0.41	2.060±0.04
F8	98±0.51	0.667±0.29	1.850±0.02	F22	128±0.47	0.665±0.27	2.023±0.02
F9	92±0.74	0.698±0.21	1.810±0.06	F23	126±0.58	0.771±0.27	2.015±0.03
F10	93±0.42	0.680±0.33	2.105±0.09	F24	83±0.67	0.784±0.28	2.100±0.04
F11	106±0.55	0.692±0.25	1.900±0.01	F25	89±0.70	0.648±0.30	1.990±0.06
F12	111±0.61	0.721±0.45	1.810±0.02	F26	94±0.69	0.658±0.29	1.184±0.08
F13	114±0.81	0.840±0.37	2.148±0.06	F27	97±0.40	0.711±0.42	1.790±0.07
F14	98±0.75	0.852±0.40	2.120±0.08				
						Pure drug - -	0.250±0.01

Each value is average of three separate determinations ±SD



**Fig. 2: Size distribution by intensity (A) and zeta potential distribution report (B) of batch F6**

of nanoparticles can be attributed to the presence of the quaternary ammonium groups of Eudragit L-100<sup>[17]</sup> (fig. 2).

Saturation solubility studies of pure drug and all batches of nanoparticles were studied in distilled water. The result of pure drug and all batches of nanoparticles were shown in Table 3. Results indicated that solubility of all batches of the nanoparticles increased as compared to pure drug<sup>[18]</sup>. SEM photograph was shown in fig. 3. SEM has shown that the nanoparticles were small, spherical and porous in nature. The SEM image of fenofibrate powder appeared as smooth-surfaced, irregularly shaped, flat crystals in shape. However, the converted solid nanoparticles appeared as smooth-surfaced particles indicating complete adsorption of lipids containing amorphous drug inside the pores of Eudragit L-100 polymer.

In fig. 1, it could be seen that the fundamental peaks were retained in the pure drug and optimized batch of nanoparticles. Presence of C-H stretching showed 2850-3000 and CH<sub>3</sub> bending at 1365 cm<sup>-1</sup>, C=O stretching of carbonyl at 1670-1820 cm<sup>-1</sup>, COO stretching at 1000-1300 cm<sup>-1</sup> confirmed the presence of drug in optimized batch of nanoparticles (F-6). Eudragit L-100 also showed carboxylic acid OH stretching and C=O stretching at 1700-1725 and 2500-3300 cm<sup>-1</sup>, respectively. CH<sub>3</sub>-CO- at around 1750, 1300, respectively showed ester as C=O stretching and alkane contains C-H stretching and C-H bending at 2850-3000 and 1350-1480, respectively. The optimized batch of nanoparticles showed identical spectrum with respect to the spectrum of the pure drug and polymers, indicating no chemical interaction or changes between the drug molecule and polymers during preparation of nanoparticles<sup>[19]</sup>. The PXRD study of nanoparticles was shown in Fig. 4. It revealed that the intensity of the peaks for the pure drug was sharp but for the drug-loaded nanoparticles, the intensities of the peaks

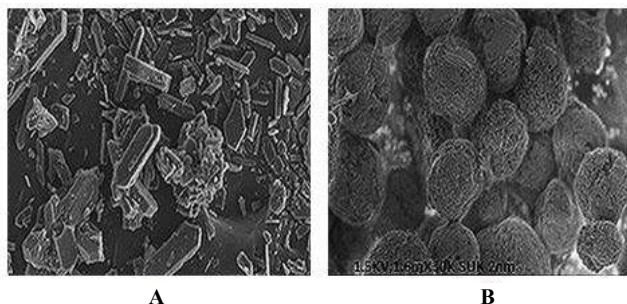


Fig. 3: Scanning electron microscopy of fenofibrate (A) and optimized batch of F6 (B)

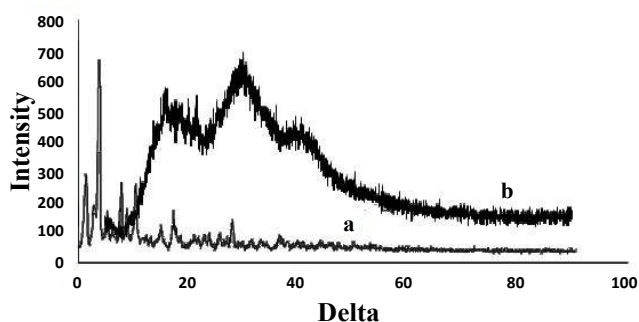


Fig. 4: X-ray diffraction pattern of fenofibrate (a) and optimized batch F6 (b)

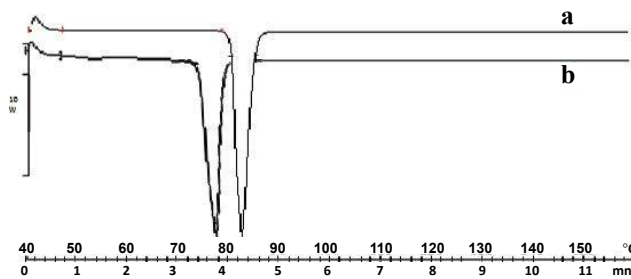


Fig. 5: DSC thermogram of fenofibrate (a) and optimized batch F6 (b)

decreased due to the reduced crystallinity of the fenofibrate<sup>[17]</sup>.

The DSC thermogram of drug and nanoparticles was shown in fig. 5. In case of pure fenofibrate, a sharp endothermic peak was observed at 82° corresponding to its melting point. In the drug-loaded nanoparticles, melting endotherm was observed at 80° with sharp appearance. This change in slightly decreasing the temperature indicated reductions the crystallinity of fenofibrate in the formulation of nanoparticles<sup>[20]</sup>.

The *in vitro* drug release profile of the formulation was in the range of 65.79±1.80 to 89.01±0.30 % for 30 min (fig. 6). The batch F6 showed the fastest dissolution rate, with approximately 89 % of the drug being released within 30 min<sup>[20]</sup>. The results obtained were subjected to multiple regression analysis using Stat-Ease (Design Expert trial, version 8.0) software. The application of response surface methodology yielded the following regression equations, which suggested an empirical relationship between the values of the responses and independent variables in coded unit were shown in fig. 7 and the particle size observed for F6 batch was 91 nm. So F6 batch was optimized as it showed good favourable results on the basis of *in vitro* drug release study, entrapment efficiency, drug loading, solubility study, particle size and practical yield.

A satisfactory attempt was made to develop nanoparticles of fenofibrate, a BCS class II drug to

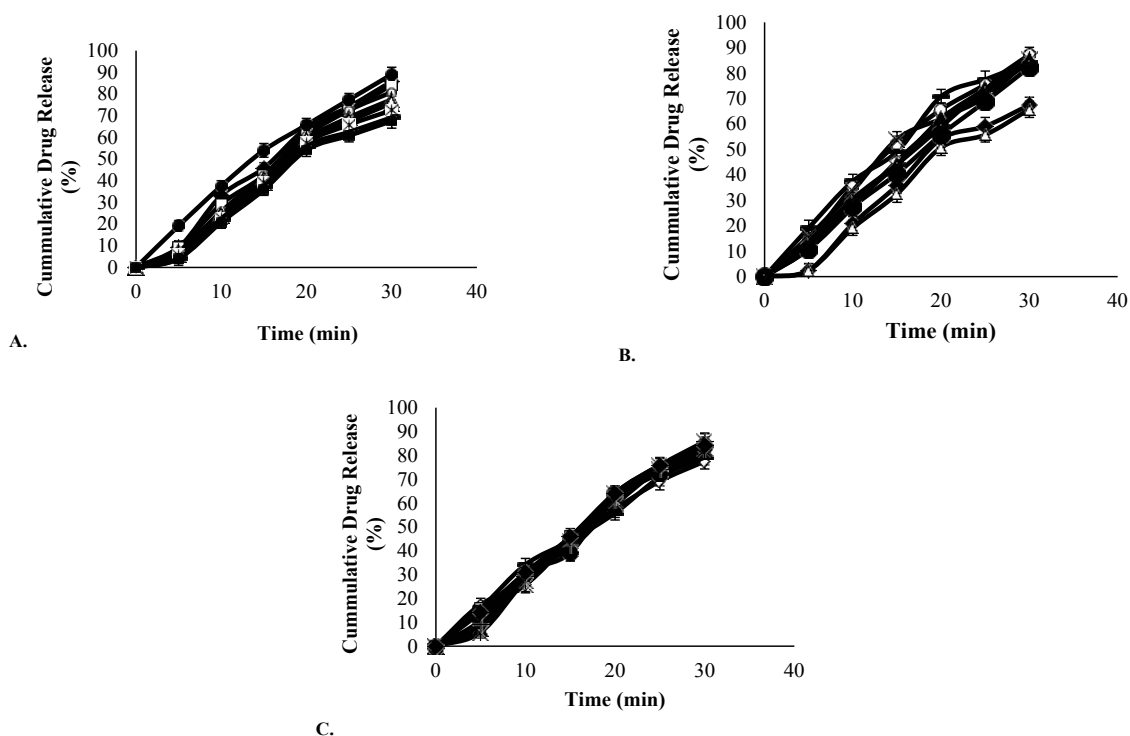


Fig.6: Drug release profile of nanoparticle batches F1 to F9 (A), F10-F18 (B) and F19-F27 (C)

A: —◆— F1; —□— F2; —○— F3; —▲— F4; —△— F5; —●— F6; —×— F7; —■— F8; —■— F9. B: —◆— F10; —△— F11; —■— F12; —○— F13; —×— F14; —□— F15; —▲— F16; —●— F17; —■— F18. C: —◇— F19; —□— F20; —■— F21; —▲— F22; —×— F23; —\*— F24; —●— F25; —I— F26; —◆— F27

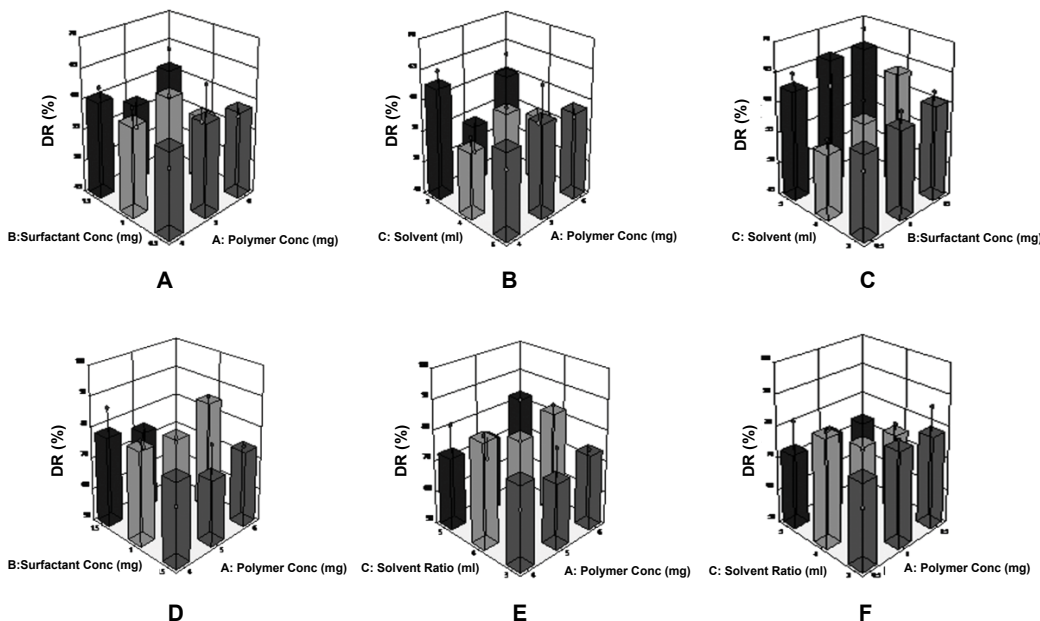


Fig. 7: % RSM factorial graphs (A to F) of nanoparticle batches F1-F27

enhance the solubility. A full  $3^3$  factorial design was used. As drug and polymer ratio increases beyond 1:6, EE, drug loading and particle size also increased but practical yield decreased. The formulation batch F6 was found to be optimized batch on the basis of size of nanoparticle, yield, encapsulation efficiency as well

as *in vitro* drug release, which was satisfactory as per requirements. The FTIR and DSC studies revealed absence of any chemical interaction between drug and excipients. Morphology was observed by SEM analysis that the nanoparticles were small and spherical in nature. Particle size observed for optimized batch

was 91 nm. Percent drug release for the optimized batch was 89.01 % at the end of 30 min. Optimized formulation for nanoparticle preparation contained 1:6 drug polymer ratio, 1:3 organic solvent ratio and 1 % surfactant. Thus, preparation of nanoparticles by precipitation method appeared to be a unique technology, which provided improved solubility and consequently increased bioavailability of BCS class II drugs that could prove to increase therapeutic effectiveness.

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### Conflicts of interest:

There are no conflicts of interest.

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