



Research Article

Compatibility Study of Fenofibrate with Some Common Excipients and Their Effect on Solid Dosage Formulation Development

Prajakta Arun Pawar¹, Vivek Ranjan Sinha¹, Ashok Kumar Yadav^{1*}

¹University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

*Corresponding to: Ashok Kumar Yadav, PhD, Assistant Professor, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160014, India; Email: ashoky@pu.ac.in

Received: December 5, 2023 Revised: June 25, 2024 Accepted: June 27, 2024 Published: July 4, 2024

Abstract

Objective: Through fenofibrate (Fen) and excipient compatibility assessments and the development of Fen pellets, the current study aims to discover suitable excipients to improve performance and stability of oral solid formulations.

Methods: Analytical instruments [Differential Scanning Calorimetry – Q20, TA Instruments, Fourier Transform Infrared Spectroscopy Spectrum RX 1, Bruker Advance Neo 500MHz Nuclear Magnetic Resonance Spectrometer, and Thin Layer Chromatography] were used to characterize Fen and to study the compatibility. Excipients and Fen were obtained from Loba chemie and Biocon, correspondingly. USP1-type dissolution apparatus was used to study the dissolution, and Auto Dock VINA 1.2.0 software was utilized to know the interaction of Fen with different excipients.

Results: Different analytical techniques confirmed that Fen was compatible with used excipients. Docking score for combination of Fen with microcrystalline cellulose (MCC) was found -2.3 and it showed minimum interaction with each other. Additionally, an instant release of Fen tablet was deliberated utilizing a combination of various excipients. Maximum drug release (93.03% in 60min) was obtained with physical mixture of Fen and MCC. Tablet batches 1, 2 and 3 showed 94%, 88% and 87% percent drug release respectively at 90min. It was observed that batch 1 displayed extreme drug release and lowest disintegration time.

Conclusion: From several analytical procedures, it was discovered that Fen was compatible with excipients used in pharmaceutical manufacturing, including lactose, magnesium stearate, MCC, talc, dicalcium phosphate, and mannitol. Physical mixture of MCC with Fen disclosed extreme amount of % drug release in shorter period. Docking studies displayed possible interactions among Fen and excipients. It was observed that Fen was more soluble when combined with the microcrystalline complex. Developed immediate release tablets demonstrated fast disintegration and drug release.

Keywords: compatibility, formulation, excipients, Fen, dissolution, molecular, docking

Citation: Pawar PA, Sinha VR, Yadav AK. Compatibility Study of Fenofibrate with Some Common Excipients and Their Effect on Solid Dose Formulation Development. *J Mod Biol Drug Discov*, 2024; 3 4. DOI: 10.53964/jmbdd.2024004.

1 INTRODUCTION

For a new dosage form to be safe, effective, and stable preformulation research is necessary^[1,2]. Investigation for the physical and chemical characteristics of the drug alone and in combination with excipients is part of this process^[3]. Drugs are prepared by mixing active pharmaceutical ingredients (API) with different excipients. Excipients are well known for maximizing capacity of product for the efficient performance of medication by accelerating the release of API, and safeguarding it from deterioration^[4]. Despite being pharmacologically inert, excipients may interact with a drug when it is administered and influence the stability of drug^[5,6]. Incompatibility is the result of the interaction between the excipient and the drug, which affects the physical and chemical qualities of the formulations^[7,8]. Effective and reliable formulations that can improve patient compliance, improve drug absorption, and lengthen shelf life require careful excipient selection^[9]. Analytical techniques must be used to properly examine any potential incompatibilities between the drug and excipient to prevent such interactions during the drug formulation development process. The current study used analytical techniques to evaluate the drug-excipient compatibility of fenofibrate (Fen) as well as the preformulation of a novel dosage form.

An anti-hyperlipidemic drug called Fen increases levels of high density lipid while reducing levels of low-density lipid, very low-density lipid, cholesterol, and triglycerides. The drug is primarily used to treat hypercholesterolemia, severe hypertriglyceridemia, and dyslipidemia^[10]. Fen increases lipolysis, activates lipoprotein lipase, and reduces apoprotein C-III through activating peroxisome proliferator activated receptor alpha. Therefore, this is commonly used drug. Lactose (LAC), mannitol, magnesium stearate (MgS), microcrystalline cellulose (MCC), talc, and dicalcium phosphate (DP) were used excipients in the current investigation. It is pertinent to perform the detailed compatibility study of Fen with these excipients as these excipients were not used for compatibility study with Fen and their solid dose formulation. Compatibility study reveals the interaction of Fen with excipient. Excipient is an important component of drug and if it interacts with API, properties of drug will change that why it is important to do compatibility study. Nuclear magnetic resonance (NMR), ultraviolet spectroscopy, differential scanning calorimetry (DSC), and fourier transform infrared spectroscopy (FTIR) were utilized to analyze the drug-excipient interaction. Fen and used excipients were characterized with different analytical techniques. To determine the drug release from of each physical mixture, a dissolution study of all physical mixtures was conducted. Additionally, *in-silico* experiments were conducted to learn more about potential interactions

between drugs and excipients, which aided *in vitro* drug release and compatibility testing. Fen compatibility experiments were carried out with LAC, talc, MCC, DP, MgS, and mannitol which were used for the formulation of conventional tablet. Several formulations of Fen are reported^[11-14]. Further, using the direct compression method, a conventional Fen tablet was formulated with compatible excipients which were studied^[15] and post-compression characterization, and *in vitro* drug release for developed tablet were investigated.

2 MATERIALS

Fen (CAS 49562-28-9) was secured from Biocon, Bangalore as a gift sample for research purpose; MgS (CAS 557-04-0), LAC (CAS 63-42-3); MCC (CAS 9004-34-6), DP (CAS 7757-93-9), talc (CAS 14807-96-6), and mannitol (CAS 69-65-8) were gained from Loba chemie Pvt. Ltd., Mumbai and Central drug house, New Delhi, respectively. The solvents were acquired from Thermo-Fischer Scientific India Pvt. Ltd. in Mumbai, India.

3 METHODS

3.1 Compatibility Study

To determine whether Fen and a few chosen excipients were compatible, a physical mixes of the medication and the excipient in a 1:1 ratio was prepared, and the results were examined using the analytical techniques listed below.

3.2 FTIR Study

The test compound's different functional groups exhibit distinct vibrational frequencies that can be identified using FTIR spectroscopy. Any variation to the bond exhibiting typical vibrational frequencies results in spectral changes, which cause the absorption peaks to divide and frequency shift, FTIR spectroscopy can be useful for evaluating the compatibility between components. Therefore, the existence of any spectrum changes during the compatibility analysis may be a sign of likely incompatibility. The test compound's different functional groups exhibit distinct vibrational frequencies that can be identified using FTIR spectroscopy. KBr disc method (sample to KBr weight ratio of 1:100) was used to obtain the FTIR spectra using Spectrum RX 1, (Perkin Elmer, U.K.) in a range of 4000cm⁻¹-500cm⁻¹^[16].

3.3 DSC Study

A DSC-Q20 from TA instruments (New Castle, USA) was used to obtain DSC thermograms of the samples. With a few changes, the procedure was used as it was described in the literature. Samples were heated under nitrogen purge from 50°C to 300°C in sealed standard aluminum pans at a

Table 1. Calibration Curve of Fen

Concentration (µg/mL)	Absorbance ± SD	Relative Standard Deviation (RSD) (%)
0	0	0
2.5	0.113±0.0019	1.72
5	0.200±0.0002	0.13
7.5	0.314±0.0040	1.28
10	0.404±0.0041	1.02
15	0.582±0.0021	0.37
20	0.774±0.0022	0.30
25	0.937±0.0017	0.18

scanning rate of 10°C/min. As a guide, an empty aluminum pan was utilized. The formation or disappearance of new endothermic peaks, a considerable shift in the melting point of the constituents, or a fluctuation in the corresponding enthalpies of reaction were all indicators of interactions in DSC thermograms^[17].

3.4 NMR Spectroscopy Study

The most common used method to examine a molecule's structure is NMR. NMR is very discriminatory method which can detect interaction via variations in chemical shift because of change in the electronic environment at the interacting atoms. NMR spectrum of Fen and its physical mixtures were recorded in DMSO-*d*₆ utilizing Bruker Avance Neo 500MHz NMR spectrometer^[18,19].

3.5 Analytical Method Development

3.5.1 UV-Visible Spectroscopy Method Development and Validation

Fen (10mg) was dissolved in ethanol to create a stock solution with a concentration of 100µg/mL. The volume was then increased to 100mL. Graded dilutions of the stock solution were used to create a standard Fen solution with a concentration range of 2.5-25µg/mL (Table 1). Using UV-visible spectroscopy, the solution's absorbance was measured at 290nm, and a calibration curve was presented in Figure 1. The calibration curve appears to be quite linear, as indicated by the correlation coefficient, or R^2 , which was determined to be above 0.99.

3.5.2 Calibration curve for Fen

Calibration curves for Fen in ethanol were developed and presented in Figure 1.

3.5.3 Linearity

It involves figuring out the drug's concentration range that complies with Beer-Lambert's Law. Standard Fen solutions with varying concentrations (2.5-25µg/mL) were utilized for linearity investigations. The calibration curves were obtained by plotting the absorbance of various

concentrations against the concentrations, following a triplicate analysis. As seen in Figures 1 and 2, the calibration curve of absorbance against concentration in ethanol and water was determined to be linear over a range of 2.5-25µg/mL. Figures 1 and 2 illustrate the regression equations, which were $y=0.0385x$ and $y=0.0354x$, where y stands for absorbance and x for concentration in µg/mL. The results of the regression reveal that $R^2=0.999$ in ethanol and $R^2=0.9957$ in water.

3.5.4 Range

The range of the method was derived from the linearity studies and provided acceptable degree of linearity and precision. The range was obtained in the range of 2.5 to 25µg/mL.

3.5.5 Interday and Intraday Precision

Closeness of two or more measurements to each other is precision. The mean absorbance of three concentration (2.5, 10, 25µg/mL) with standard deviation and relative standard deviation were calculated and given in the Table 2. In case of intraday precision, percent RSD values were found in the range of 0.52%-1.60% and, whereas of interday precision, it was obtained in the range of 0.64%-1.89%. These results were within the permissible limit i.e., <2% and thus validated the precision.

3.6 Thin Layer Chromatography (TLC) Study

The basis of TLC is the dispersion of a chemical between an eluting solvent-moving liquid phase and a thin layer of applied solid material on a glass or plastic plate. A sensitive and quick method known as TLC is used to count the components in a mixture, confirm the purity and identity of compound, track the progression of a reaction, and analyze fractions obtained from column chromatography^[20]. TLC consists of the following three steps: spotting, TLC plate creation, and visualization. Using a glass capillary spotter, a little amount of diluted solution is applied to one end of the TLC plate to perform spotting. When developing a TLC plate, the bottom of the plate is submerged in the development solvent, which then rises through capillary action. In this work, a 9:1 chloroform:methanol as mobile phase was employed. Samples ascend upward at different speeds and mix with the starting spot along the way due to differences in their solubility in the solvent and variations in their attraction to the stationary phase. Visualization can be achieved with UV light. The spot stands out against the bright background because the silica gel on the plate has been impregnated with a fluorescent material that lights when exposed to UV radiation. A TLC plate was also used for visualization by being placed inside a closed container of iodine vapor^[21]. Following visualization, R_f values were determined.

3.7 In Vitro Dissolution Study

The USP-II types dissolving instrument (Lab India DS

Fenofibrate Calibration Curve

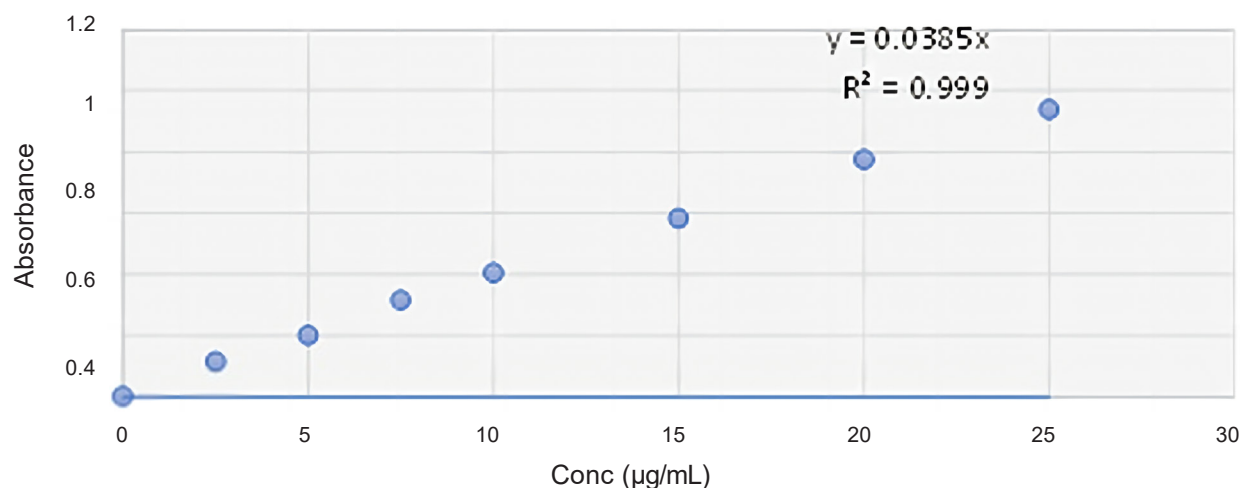


Figure 1. Calibration Curve of Fen in Ethanol.

Fenofibrate Calibration Curve

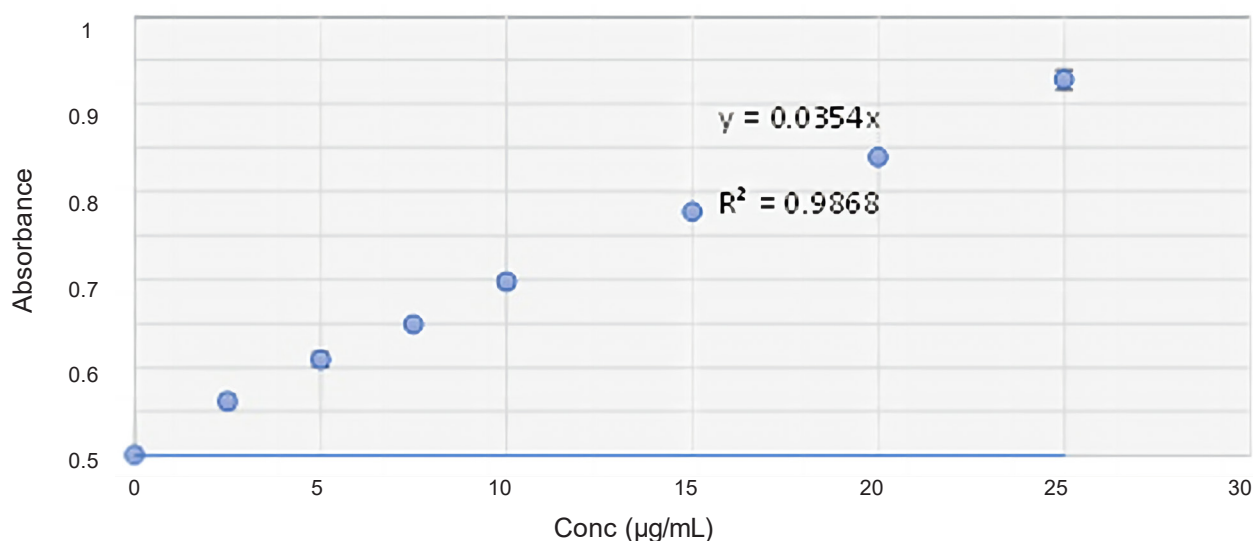


Figure 2. Calibration Curve of Fen in Water.

Table 2. Interday and Intraday Precision

Conc (µg/ml)	Intraday Precision		Interday Precision	
	Mean Absorbance±SD	RSD (%)	Mean Absorbance±SD	RSD (%)
2.5	0.113±0.1131	0.52%	0.116±0.0021	1.89%
10	0.425±0.0066	1.60%	0.409±0.0043	1.07%
25	0.944±0.0055	0.59%	0.926±0.0060	0.64%

800), India, was utilized to conduct the dissolution study. A copper wire was used to secure the capsule containing 200mg of Fen to the paddle after it had been precisely weighed and filled. As a dissolving medium, 900mL of 0.05M sodium lauryl sulphate (SLS) in distilled water were used. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$, and the stirring speed was 75rpm. Five millilitres of samples were removed from each beaker at various periods and replaced with fresh media in order to maintain the sink condition. After passing through a $0.2\mu\text{m}$ nylon filter, the extracted

samples were measured at 290nm using a 3,200UV/Visible Spectrophotometer. In accordance with the medication % dissolved in the dissolving media, the release statistics were assessed. As previously mentioned, dissolving tests were also carried out for drug-excipient physical combinations^[22,23].

3.7.1 Molecular Docking

A proven *in-silico* method to identify drug interactions on the molecular level is known as “molecular docking”^[24,25]. The Auto Dock VINA software was used for the docking process. The PubChem database provided the 2D structures of the compounds that were downloaded. The docking structures were assembled using the Auto Dock tools, and a blind docking with a $40\text{\AA} \times 40\text{\AA} \times 40\text{\AA}$ grid size was completed.

3.7.2 Formulation Development of Conventional Tablet

Direct compression is quickly emerging as one of the most widely used and economical tablet production

Table 3. Composition for Conventional Tablet of Fen

Ingredients	Quantity (mg)		
	Batch1	Batch2	Batch3
Fen	120	120	120
MCC	142	-	-
Anhydrous LAC	-	142	-
DP	-	-	142
MgS	3	3	3
Sodium starch glycolate	4	4	4
Talc	6	6	6
Total	275	275	275

Table 4. Dissolution Test Parameters

Dissolution Media	900mL of 0.5M SLS in Water
Temperature	37±0.5°C
Stirring speed	75rpm
Tablet taken	One tablet in each basket
Volume with drawn	5mL in specific interval of time
$\lambda_{\max}$	280nm

techniques in the pharmaceutical industry. The term “direct compression” refers to the method of compressing tablets into a firm compact straight from a powdered active drug component and appropriate excipients, without using the granulation process. As a directly equivalent vehicle, MCC and DP were employed^[26-28].

3.7.3 Conventional Tablet of Fen

Every component was precisely weighed and put through 40-number mesh sieves. In an inflated polythene bag, the necessary amount of Fen is combined with the disintegrant and diluent, and thoroughly mixed for ten to fifteen min. For consistent API mixing, geometric mixing was employed. Furthermore, talc and MgS were added to the powder combination to lubricate it. Using a rotary tableting machine, flat faced direct compression tablets (275mg) were created. Table 3 contained the typical tablet formulation formula for each batch.

The following variables were assessed in post-compression investigations for the Fen pills that were formulated.

3.7.4. Appearance

Uncoated tablets were kept in the light and viewed via a lens for determining the shape and color of the tablet.

3.7.5 Hardness Test

A tablet’s resistance to mechanical shocks during handling is demonstrated by a hardness test^[15,28]. Monsanto hardness tester was utilized to know the tablet’s hardness. It was stated as kg/cm². Tablets were chosen at random and examined for hardness. The values of the mean and

standard deviation were ascertained.

3.7.6 In-Vitro Disintegration Time

The *in-vitro* disintegration time of the produced tablet was determined using the Lab India disintegration instrument. The disintegration time is the length of time needed for a tablet to dissolve and leave no trace of solid material behind. Water was employed as the immersion liquid and maintained at 37±2°C. as a disintegration medium. Using a disintegration test instrument in accordance with I.P. requirements, the tablet’s *in-vitro* disintegration time was ascertained.

3.8 In-Vitro Dissolution Study

An easy, quick, and accurate method for evaluating the quality of formulations is an *in-vitro* dissolution study^[29]. The release of the medication from the prepared formulation at different times was the primary goal of the *in vitro* dissolving test. The *in vitro* dissolution test for each formulation was conducted using the following parameters, which are detailed in Table 4 and were used throughout the investigation.

4 RESULTS

4.1 FTIR Spectroscopy

The distinguishing absorption bands of the Fen and excipients were displayed in the FTIR spectra, which are displayed in Figure 3A-E for the drug and mixture of drug and excipients. Fen’s FTIR spectra are similar to previously published FTIR spectra of the compound because of the absorption peaks at 2883cm⁻¹ (C-H stretch), 1598cm⁻¹ (C=O stretch), and 1728cm⁻¹ (ester stretch)^[16,30]. Additionally, a comparison of the FTIR bands of physical mixtures containing various excipients and pure Fen was conducted, as Table 5 illustrates. The distinct absorption bands of pure Fen and physical mixes of Fen with varying excipients are seen at the same location in Table 5 and Figure 3. Fen is thus compatible with every excipient that is utilized.

4.2 ¹H NMR Spectroscopy

¹H NMR has been used in several investigations to find any drug-excipient interactions^[18,19,31]. The chemical shift (δ) of 1.16 δ (CH-CH₃), 1.60 δ (C-CH₃), and 4.98 δ (CH₃-CH) were the distinctive values of the signals found in the ¹H NMR spectrum of Fen, which is identical to the spectrum that has been published^[32]. Table 6 presents the results of the comparative examination of the chemical shifts of the Fen and physical combinations, as well as the comparison of the chemical shifts of the two spectra. It was found that the typical signals of mixes of Fen including various excipients and pure Fen are similar. Fen and the employed excipients were hence compatible. Figure 4 depicted the Fen structure.

4.3 DSC Study

The DSC thermogram of Fen showed a single endothermic peak at 81.74°C (Figure 5A), which was

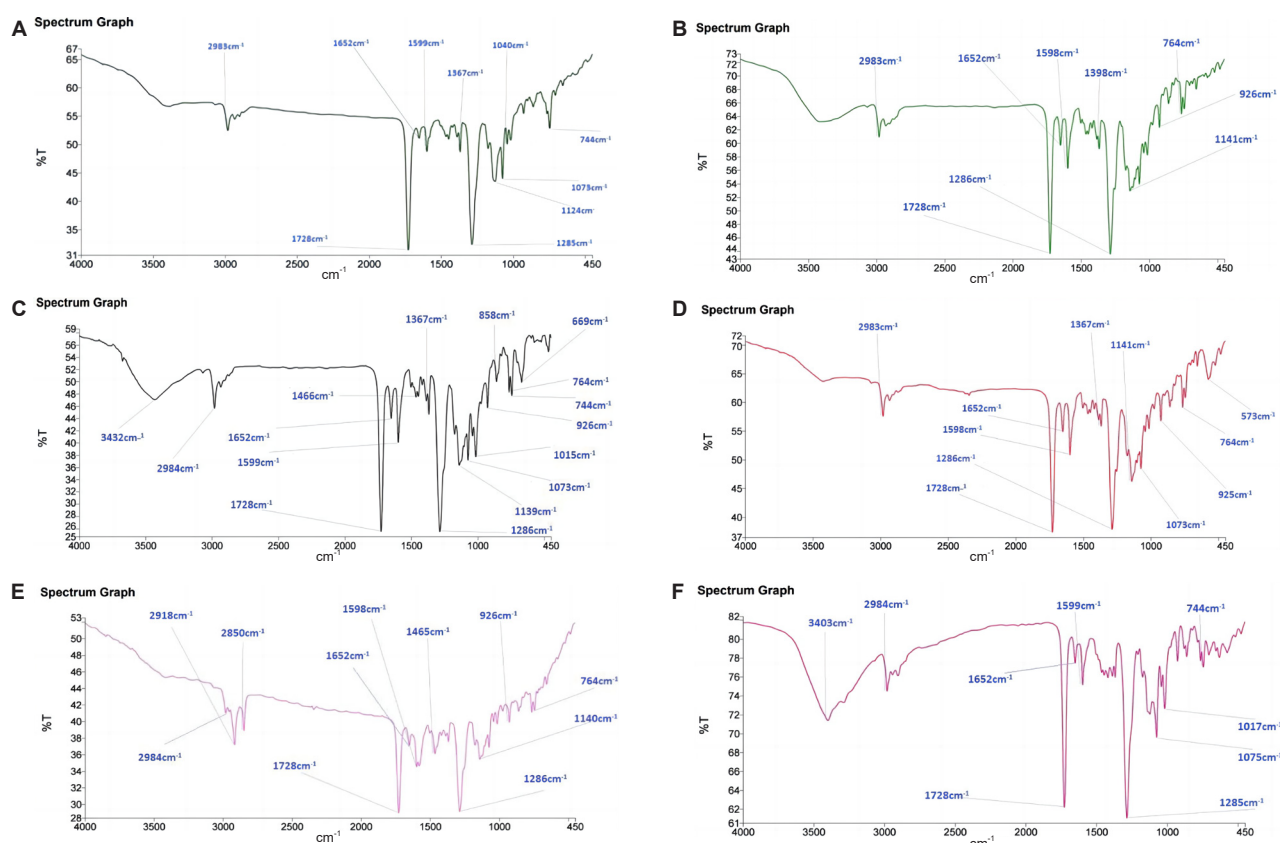


Figure 3. FTIR Spectra for Fen with LAC (3A); MCC (3B); Talc (3C); DP (3D); Mg Stearate (3E); and Mannitol (3F) and Physical Mixtures of Fen and corresponding Excipients.

Table 5. A Comparative Study for the FTIR Absorption Bands of Pure Fen and Physical Mixture of Fen with Different Excipients

Functional Group	Feno	Feno + DP	Feno + MCC	Feno + LAC	Feno + Talc	Feno + Mannitol	Feno + MgS
C-H stretch	2983	2983	2983	2983	2984	2984	2984
C=O	1598	1598	1598	1599	1599	1598	1598
Ester	1728	1728	1728	1728	1728	1728	1728

Table 6. ¹H NMR Chemical Shifts for Fen and Physical Mixtures of Drug and Excipients

Position of Proton	Chemical Shift	Feno - Fibrate	Fen + LAC	Fen + MCC	Fen + Talc	Fe + DP	Fen + Mannitol	Fen + MgS
1	CH ₃ -CH	1.16	1.16	1.16	1.16	1.16	1.16	1.16
3	CH ₃ -C	1.60	1.60	1.60	1.60	1.60	1.60	1.60
2	CH-CH ₃	4.98	4.98	4.98	4.98	4.98	4.98	4.98

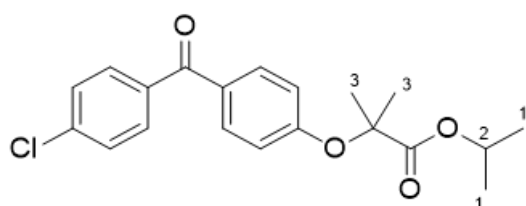


Figure 4. Structure of Fen: 1, 2, 3 Represent Position of Protons.

determined to be consistent with the literature that has been published^[17,32]. The DSC thermograms of a physical

mixture of LAC, MCC, talc, MgS, DP, and mannitol, as well as pure Fen, were displayed in Figure 5.

4.4 TLC Study

The amount that the materials travel down the plate is measured using the R_f value. R_f is calculated by dividing the substance's travel distance by the solvent's travel distance. Its value is consistently in the range of 0 and 1. Fen and its physical combinations with several excipients (LAC, MCC, talc, DP, MgS, and mannitol) were shown to have an R_f value of 0.56^[33].

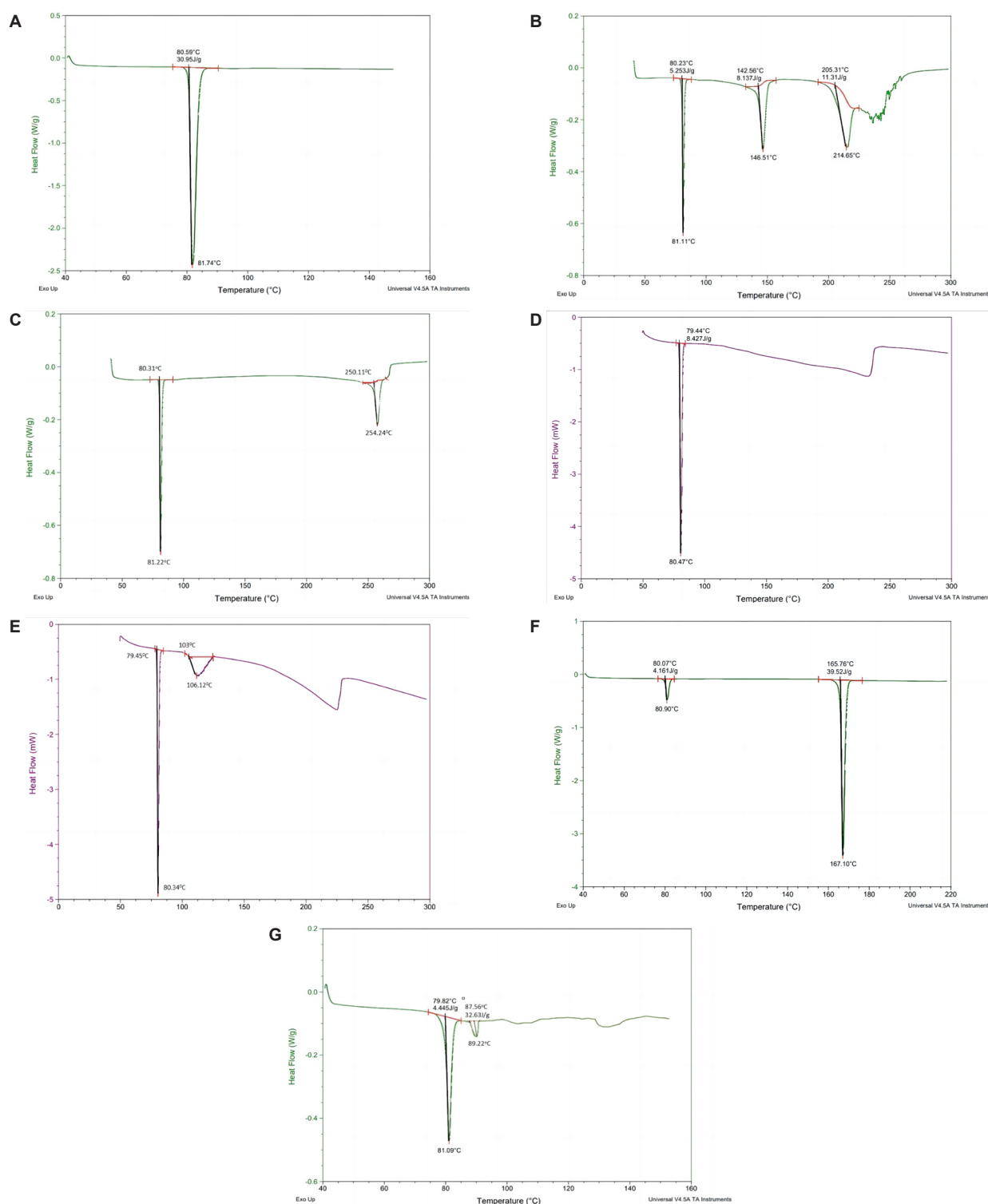


Figure 5. DSC Thermograms: Fen (A); Physical Mixtures of Fen and LAC(B); Physical Mixtures of Fen and MCC (C); Physical Mixtures of Fen and Talc (D); Physical Mixtures of Fen and DP (E); Physical Mixtures of Fen and Mannitol (F); Physical Mixtures of Fen and MgS (G).

4.5 In-Vitro Drug Release for Physical Mixtures of Fen and Excipients

Figure 6 shows the Fen dissolving behavior for physical combinations with various excipient types attached. For 40min, the dissolving behavior of pure Fen in physical mixes with several excipient types was observed. It was shown that the minimum drug release for 60min when Fen was combined with MgS was 46.29%, whereas the highest drug release for 60min when Fen was combined with MCC was

93.06%. This was caused by the hydrophobic properties of the MgS; however, the hydrophilic properties of MCC allowed for more drug release. Therefore, choosing the excipient wisely will guarantee that the formulation performs well.

4.6 Molecular Docking

Table 7 provided the number of hydrogen bonds and docking score for each complex (Fen with various excipients), and Figure 7 included information on the 3D posture of

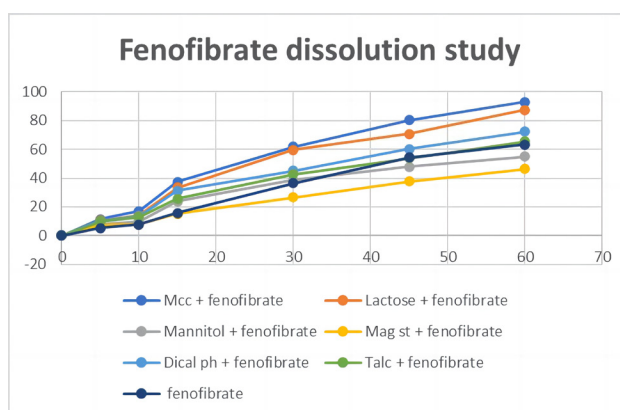


Figure 6. In-Vitro Dissolution Study for Fen and Physical Mixtures of Drug and Excipients.

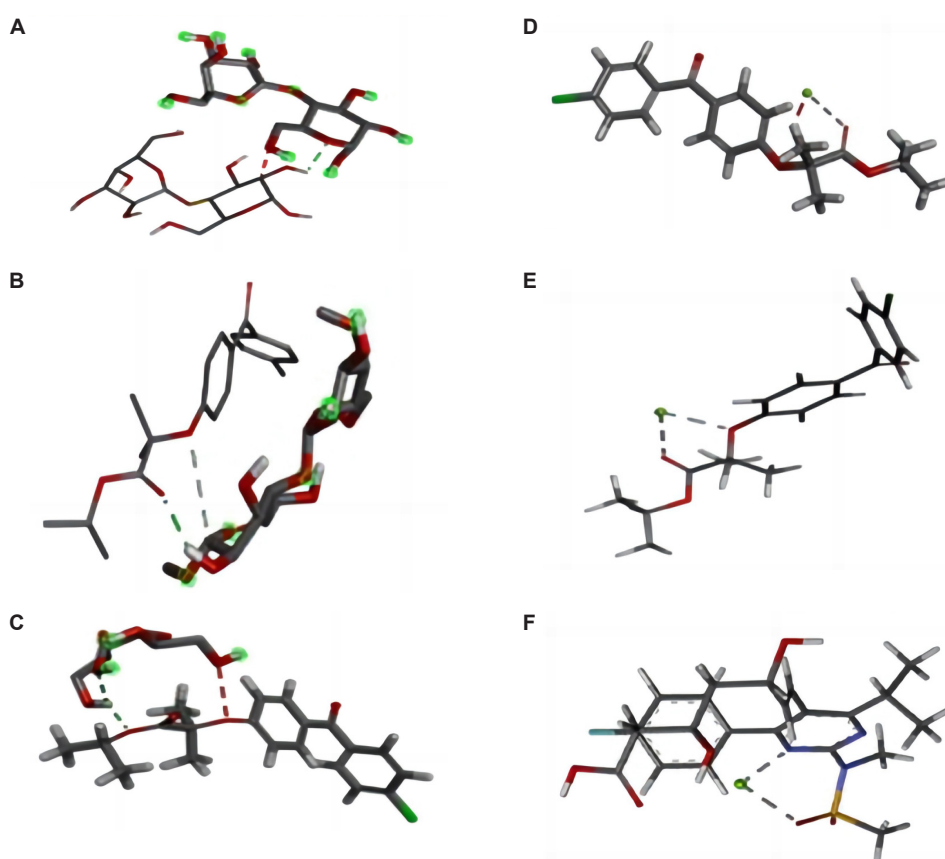


Figure 7. Docked Pose of Fen with: A-Anhydrous LAC Complex; B-MCC Complex; C-Mannitol Complex; D-MgS Complex; E-Talc Complex; F-DP Complex.

docked complexes. Docking scores for complexes of Fen with LAC, MCC, mannitol, MgS, talc and DP were observed as -2.4, -2.3, -2.9, -3.1, -2.5 and -2.5, respectively and numbers of hydrogen bonds are 2 for each complex (Table 7).

4.7 Formulation Development of Conventional Tablet

4.7.1 Post-Compression Study

4.7.1.1 Appearance

Upon examination, the tablets from each batch were discovered to be flat, circular, and crack-free, with a whitish tint. By selecting the three tablets at random, the thicknesses of the tablets for each formulation were measured with a dial caliper. For batches 1, 2, and 3, the mean tablet thickness values were discovered to be 4.2mm, 4.0mm, and

4.4mm, respectively. By selecting three tablets at random, the Monsanto hardness tester was used to measure the hardness of each formulation's tablets. The mean values for batches 1, 2, and 3 were found to be 3.5kg/cm², 3.1kg/cm², and 3.2kg/cm², respectively.

4.7.1.2 Disintegration Profile for Fen Oral Formulation

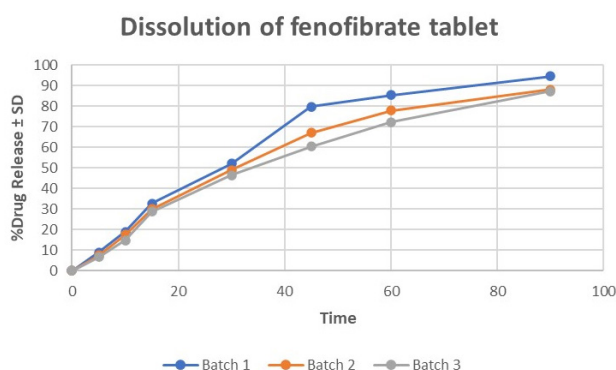
Analysis of disintegration for three batches Batches 1, 2, and 3 were selected at random from each batch, and the disintegration times for those batches were discovered to be 2, 4, and 4min, respectively.

4.7.1.3 In Vitro Dissolution Studies of Formulated Tablet

Further, *in-vitro* %drug release study was performed

Table 7. Docking Score and No. of H-Bonds

S.No	Drug + Excipient	Docking score	No of H-bond
1	Fen + Anhydrous LAC	-2.4	2
2	Fen + MCC	-2.3	2
3	Fen + mannitol	-2.9	2
4	Fen + MgS	-3.1	2
5	Fen + Talc	-2.5	2
6	Fen + DP	-2.5	2


Figure 8. Dissolution Profile of Fen Tablet.

in water and *in vitro* dissolution studies of the formulated tablet was shown in the Figure 8. The dissolution behavior of batches for formulated Fen tablet were studied for 90min. The percentage of drug released in 15min for each of the three batches was found to be quite similar: batch 1 showed 32% of the drug released, batch 2 showed 30%, and batch 3 showed 28%. After 90min, it was discovered that the medication release percentages for batches 1, 2, and 3 were 94%, 88%, and 87%, respectively.

5 DISCUSSION

5.1 Compatibility Studies Using FTIR Spectroscopy

The FTIR spectrum of pure Fen was characterized by absorption bands at 2983 (alkane stretch C-H), 1598 (C=O) and 1728 (ester) cm^{-1} . FTIR spectrum of physical mixture of Fen with anhydrous LAC showed the characteristic absorption peaks [2983 (alkane stretch C-H), 1599 (C=O) and 1728 (ester) cm^{-1}]. When FTIR spectrum of pure Fen was compared with the FTIR spectrum physical mixture of Fen with LAC, it was found that the peak corresponding to pure Fen and physical mixture with anhydrous LAC were reserved (Figure 3A). It means that there was no interaction between drug and anhydrous LAC and if there was any interaction between drug and anhydrous LAC, there will be shift of absorption peaks. Therefore, it was determined that Fen and LAC did not interact chemically. Further investigation revealed the distinctive peaks [2983 (alkane stretch C-H), 1598 (C=O), and 1728 (ester) cm^{-1}] in the FTIR spectrum for the physical mixing of Fen and MCC. The bands corresponding to pure Fen and MCC were found to be kept at the same position when spectra of pure Fen

and a physical mixture of Fen with MCC were compared. As a result, we anticipated that Fen and MCC would not interact chemically. (Figure 3B). FTIR spectrum for physical mixture of Fen with talc showed the characteristic bands [2984 (alkane stretch C-H), 1599 (C=O) and 1728 (ester) cm^{-1}]. The physical mixture spectrum showed that the bands corresponding to pure Fen and the physical mixture of Fen and talc were located at the equivalent position, indicating that it was not possible to see any chemical interaction between the two compounds (Figure 3C). FTIR spectrum physical mixture of Fen with DP displayed characteristic bands at [2983 (alkane stretch C-H), 1598 (C=O) and 1728 (ester) cm^{-1}]. After comparing the two spectra, we discovered that the bands belonging to pure Fen were reserved, indicating that Fen and DP were not chemically incompatible (Figure 3D). Additionally, an FTIR spectra of a physical mixture of mannitol and Fen was obtained, revealing three distinct bands at [2984 (C-H alkane stretch), 1598 (C=O), and 1728 (ester) cm^{-1}]. When the two FTIR spectra were compared, the analogous band to pure Fen was observed at the same location, indicating that mannitol and Fen did not interact chemically (Figure 3E). When the physical mixture of MgS and Fen was analyzed, the FTIR spectrum revealed three distinct bands: 1728 (ester) cm^{-1} , 1598 (C=O), and 2984 (alkane stretch C-H). Given that bands of Fen were preserved in the physical mixture, this discovery demonstrated the compatibility of Fen with MgS (Figure 3F). When MgS, LAC, talc, LAC, mannitol, and DP were physically mixed with Fen, the characteristic bands of the functional groups of pure Fen were still present, according to the FTIR spectra. This suggested that Fen and physical combinations of Fen with excipients were compatible. These results demonstrated that all of the excipients that were used, such as mannitol, LAC, MgS, talc, and MCC, were compatible with Fen.

5.2 Compatibility Studies Using ^1H NMR Spectroscopy

^1H NMR has been used in a number of studies to find any drug-excipient interactions^[18,19]. Table 6 provided a description of the comparative analysis for chemical shifts of the physical mixes and Fen. The most important signals for Fen were 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -). ^1H NMR spectra of physical mixtures of Fen with anhydrous LAC, MCC, talc, DP, mannitol and MgS showed the characteristic signals at 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), 1.16 (CH_3 -CH-), 1.60 (CH_3 -C), and 4.98 (CH - CH_3 -), respectively (Table 6). There were no incompatibilities between the medication and the physical mixtures of Fen with excipients, as indicated by the ^1H NMR spectra of the physical mixtures of LAC, MCC, talc, DP, mannitol, and MgS, which all kept the distinctive signals of pure Fen. Based on the information gathered, we concluded that Fen was safe to use with all of the excipients, which included mannitol, LAC, MgS, talc, and MCC.

5.3 Compatibility Studies Using DSC

DSC thermogram of pure Fen demonstrated an endothermic peak at 81.74°C (Figure 5A). DSC thermogram of physical mixes of Fen with anhydrous LAC shown endothermic peaks at 81°C, 146.51°C and 214.65°C. When the thermograms of Fen and LAC were compared, it was found that the peaks representing pure Fen and anhydrous LAC were slightly altered, indicating that there was no chemical interaction between the two (Figure 5B). Moreover, the DSC thermogram of the physical mixture of Fen with MCC showed endothermic peaks at 81.09°C and 254.24°C. Upon comparing the two thermograms, it was observed that the peak denoting pure Fen had remained intact, albeit with minor alterations. This suggests that there was no chemical incompatibility between the drug and excipient (Figure 5C). On the DSC thermogram, the physical mixture of talc and Fen showed an endothermic peak at 80.47°C. The fact that the peak corresponding to pure Fen was found at the same place with a slight variation (Figure 5D) indicates that there was no detectable chemical interaction between talc and Fen. Physical combinations of Fen and DP showed endothermic peaks at 81.09°C and 106°C on the DSC thermogram. After comparing the two thermograms, we discovered that the peak representing pure Fen was reserved with a small variation, indicating that Fen and DP were not chemically incompatible (Figure 5E). In addition, a DSC thermogram of a physical mixture of mannitol and Fen was taken, and endothermic peaks were seen at 167 and 80.90 degrees Celsius. There was no chemical interaction between mannitol and Fen, as shown by the slightly altered matching peak to pure Fen on the comparison of the two thermograms (Figure 5F). When a physical mixture of MgS and Fen was investigated using a DSC thermogram, endothermic peaks were seen at 81.09 and 89.22 degrees Celsius. The fact that the peak of Fen was maintained with only minor changes indicates that Fen and MgS are compatible. (Figure 5G).

5.4 TLC study

The movement of material along plate is measured to determine the R_f value. The distance moved by the substance divided by travel distance of solvent is recognized as R_f . The mobile phase used in this work was a 9:1 chloroform:methanol solution. R_f values of 0.56 were obtained for Fen and physical mixes containing various excipients, like MgS, LAC, mannitol, MCC, talc, and DP. Every physical composition with a different excipient was visible at the same location as the Fen spot. This indicates that there was no interaction between the Fen and any of the physical combinations including various excipients; if there had been an interaction, the R_f value would have varied.

5.5 In-Vitro Drug Release for Physical Mixtures of Fen and Excipients

Figure 6 depicted the Fen dissolving behavior for physical combinations with various excipient types. Fen's

medication release was shown to vary depending on the excipient employed. The drug release increased together with the passage of time. The physical combination of MCC and Fen demonstrated the highest possible drug release in 60min, or 93.03%. Because LAC is hydrophilic, it also demonstrated a high drug release rate of 87.47% in 60min. However, due to their hydrophobic nature, physical combinations of Fen with talc and MgS only demonstrated 46.29% and 65.41% drug release in 60min. As seen in Figure 6, the dual effects of the various excipients' hydrophobicity and hydrophilicity affected the drug release from the physical mixes comprising different excipients.

5.6 Molecular Docking

Molecular docking is a validated in-silico method to find drug interactions at the molecular level^[24,25]. Docking tests were conducted to investigate potential interactions between Fen and various excipients. The docking analysis also displays the conformations with the lowest energy. The Fen molecule was docked with a number of excipients, including MgS, mannitol, anhydrous LAC, talc, DP, and MCC. The docking results were listed in Table 7, and Figure 7 additionally included information on the 3D pose of the docked complexes. Docking scores of complexes of Fen and excipients like LAC, MCC, mannitol, MgS, talc and DP were observed as -2.4, -2.3, -2.9, -3.1, -2.5 and -2.5, respectively and numbers of hydrogen bonds are 2 for each complex (Table 7). Comparing the docking data, it was discovered that the highest energy conformer i.e., combination of Fen with MCC disclosed minimum interaction with each other. Thus, in the dissolution study, drug release for combination of Fen with MCC was observed maximum. Docking score for complex of Fen with MgS was observed -3.1 which showed that this complex is more stable. Therefore, % drug release was found least (46%) for the physical mixture of Fen with MgS.

5.7 Formulation Development of Conventional Tablet

5.7.1 Post-Compression Study

5.7.1.1 Appearance

Tablets were found in whitish color and flat circular shape.

5.7.1.2 Thickness Test

Using a dial caliper, the thickness of each formulation's tablet was measured by selecting three tablets at random. The mean values of the thickness of tablet were found to be 4.2mm, 4.0mm, and 4.4mm for batches 1, 2 and 3, respectively. By selecting three tablets at random, the Monsanto hardness tester was used to measure the hardness of each formulation's tablets. The mean values for batches 1, 2, and 3 were found to be 3.5kg/cm², 3.1kg/cm², and 3.2kg/cm², respectively.

5.7.1.3 Disintegration Profile for Fen Oral Formulation

Random selection of tablets of three batches 1, 2 and

3 were done from each batch for disintegration study and disintegration times of batches 1, 2 and 3 were observed to be 2, 4, and 4min, respectively.

5.7.1.4 *In Vitro* Dissolution Studies for Formulated Tablet of Fen

An *in-vitro* %drug release experiment was conducted in water. USP dissolving testing apparatus-2 (paddle method) (Lab India) was used to determine the drug release of prepared batches (24). Using 900mL of 0.05M SLS in water at $37\pm0.05^{\circ}\text{C}$ and 75rpm, the dissolution test was carried out. Within the dissolving device, a sample of the solution was taken out at predetermined intervals and replaced with new dissolving medium. After the samples were filtered, their absorbance at 290nm was measured using a double beam UV spectrophotometer (UV-3200, Lab India). A % drug release was computed. On the formulations of batches 1, 2, and 3, *in vitro* dissolving tests were conducted. The plotting and analysis of the comparative dissolution graphs was done. It was discovered that all three batches had somewhat comparable amounts of medication released in 15min: batch 1 had 32%, batch 2 had 30%, and batch 3 had 28%. The amount of time increased with the drug release. After 90min, it was discovered that batches 1, 2, and 3 had released 94%, 88%, and 87% of the drug, respectively. Batch 1 had the highest quantity of drug release since MCC was present. Although the three batches should all be required for medication release, the excipients' characteristics varied after 30min (Figure 8).

6 CONCLUSION

The compatibility studies for physical mixes of Fen with different commonly used excipients such as DP, MCC, talc, LAC, mannitol, and MgS were studied by IR and NMR and it was observed that the distinctive peaks in the NMR and IR spectroscopy data were found to be unchanged or slightly off. Additionally, DSC analysis was performed on pure Fen and physical mixtures of Fen containing all excipients employed. The results showed that the endothermic peak of Fen in the physical mixture of Fen and excipient was located in the same spot. Fen was shown to be compatible with all of the excipients employed in this investigation based on the results of the DSC research. The drug dissolution performance of Fen was observed. Physical mixture of MCC with Fen showed maximum amount of drug release in shorter period. Docking studies were carried out to get the probable interactions among Fen and excipients. It was observed that Fen was more soluble when combined with the microcrystalline complex. According to all the research mentioned above, there was no interaction between Fen and the excipients. As a result, Fen and the employed excipients got along well. The development of Fen conventional tablets with suitable excipients was carried out. Conventional Fen pills are expected to dissolve rapidly in the gastrointestinal tract because of their fast disintegration. Fen batches 1, 2, and 3 had disintegration times of 2min, 4min, and 4min,

respectively. At 90min, the percentage of drug released for batches 1, 2, and 3 was 94%, 88%, and 87%, respectively. Based on the investigation, batch 1 had the highest drug release and the shortest disintegration time.

Acknowledgements

The DST-FIST Lab, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, was appreciated by the authors for allowing them to use its space.

Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Pawar PA was responsible for methodology, Sinha VR was responsible for planning, Yadav AK was responsible for concept and supervision

Abbreviation List

API, Active pharmaceutical ingredients
DP, Dicalcium phosphate
DSC, Differential scanning calorimetry
Fen, Fenofibrate
FTIS, Fourier transform infrared spectroscopy
LAC, Lactose
MCC, Microcrystalline cellulose
MgS, Magnesium stearate
NMR, Nuclear magnetic resonance
TLC, Thin layer chromatography

References

- [1] Patel P, Ahir K, Patel V et al. Drug-excipient compatibility studies: First step for dosage form development. *Pharm Innov J*, 2015; 4: 14.
- [2] Ahirwar K, Shukla R. Preformulation studies: A Versatile tool in formulation design. *IntechOpen*, 2023.[DOI]
- [3] Jabeen A, Nasir AM, Afaq B et al. An overview of pharmaceutical excipients: Interactions and incompatibilities in dosage form development. *Pharma Res J*, 2022; 1: 65-72.
- [4] Narang AS, Boddu SHS. Introduction: Excipient applications in formulation design and drug delivery. In: *Excipient Applications in Formulation Design and Drug Delivery*: Springer, 2015; 1: 1-10.
- [5] Chadha R, Bhandari S. Drug-excipient compatibility screening—role of thermoanalytical and spectroscopic techniques. *J Pharmaceut Biomed*, 2014; 87: 82-97.[DOI]
- [6] Fiorota AB, Xaviera TP, Yoshidab MI et al. Drug-excipient compatibility assessment of solid formulations containing meloxicam. *Eur J Pharm Sci*, 2018; 112: 146-151.[DOI]
- [7] Murillo-Fernández MA, Montero-Zeledón E, Abdala-Saiz A et al. Interaction, and compatibility studies in the development of olmesartanmedoxomil and hydrochlorothiazide formulations under a real manufacturing process. *Pharm*, 2022; 14: 424.[DOI]
- [8] Monajjemzadeh F, Hassanzadeh D, Valizadeh H et al. Compatibility studies of acyclovir and LAC in physical mixtures and commercial tablets. *Eur J Pharm Biopharm*,

- 2009; 73: 404-413.[DOI]
- [9] Chaurasia G. A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. *Int J Pharm Sci Res*, 2016; 7: 2313-2320.
- [10] Nguyen TN, Park JS. Exploring fenofibrate formulations for the treatment of lipid disorders: Past, Present, and Future. *Cardiometab Syndr J*, 2022; 2: 77-95.[DOI]
- [11] Atneriya U, Kapoor D, Sainy V et al. In Vitro profiling of fenofibrate solid dispersion mediated tablet formulation to treat high blood cholesterol. *Ann Pharm Françaises*, 2022; 81: 284-299.[DOI]
- [12] LingH, Luoma JT, Hilleman D. A review of currently available fenofibrate and fenofibric acid formulations. *Cardiol Res*, 2013; 4: 47.[DOI]
- [13] Jadhav N, Pawar M, Vavia P. Pickering dry emulsion system for improved oral delivery of fenofibrate. *AAPS Pharm Sci Tech*, 2022; 23: 168.[DOI]
- [14] Dabeer AA, Mishra DK, Farooqui N et al. Formulation, and evaluation of orodispersible tablet of poorly water-soluble drug “fenofibrate” by using solubility enhancement technique. *Asian J Pharm Tech*, 2021; 11: 279-283.[DOI]
- [15] Kumar R, Patil S, Patil M et al. Formulation Evaluation of Mouth Dissolving Tablets of Fenofibrate Using Sublimation Technique. *Int J Chem Tech Res*, 2009; 1: 840-850.
- [16] Volpati D, Aoki PH, Alessio P et al. Vibrational spectroscopy for probing molecular-level interactions in organic films mimicking biointerfaces. *Adv Colloid Interfac*, 2014; 207: 199-215.[DOI]
- [17] Krishna BJ, Satynarayana J, Rao NR. Rivaroxaban: Compatibility with pharmaceutical excipients using DSC and FTIR spectrophotometry. *J Pharm Res Int*, 2022; 34: 43-50.[DOI]
- [18] Tishmack PA, Bugay DE, Byrn SR. Solid-state nuclear magnetic resonance spectroscopy-pharmaceutical applications. *J pharm sci*, 2003; 92: 441-474.[DOI]
- [19] Bramham JE, Podmore A, Davies SA et al. Comprehensive assessment of protein and excipient stability in biopharmaceutical formulations using ¹H NMR spectroscopy. *Acs Pharmacol Transl*, 2021; 4: 288-295.[DOI]
- [20] Peter E. Thin-Layer Chromatography: A Modern Practical Approach. Cambridge University Press: London, UK, 2005.
- [21] Geiss F. Fundamentals of thin layer chromatography. *Anal Chem*, 1988; 60: 6723641.
- [22] Górniak A, Czapor-Irzabek H, Złocińska A et al. Screening of fenofibrate-simvastatin solid dispersions in the development of fixed-dose formulations for the treatment of lipid disorders. *Pharm*, 2023; 15: 603.[DOI]
- [23] Górniak A, Wojakowska A, Karolewicz B et al. Phase diagram and dissolution studies of the fenofibrate–acetylsalicylic acid system. *J Therm Anal Calorim*, 2011; 104: 1195-1200.[DOI]
- [24] Çinar I, Aksoy İ, Güler G. Spectroscopic and computational molecular docking studies on the protein-drug interactions: Proceedings of the Medical Technologies Congress. Antalya, Turkey, 19-20 November 2020.[DOI]
- [25] Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. *Int J Mol Sci*, 2019; 20: 4331.[DOI]
- [26] Chavan H, Chhabra G, Gujarathi N et al. Comparative study of in-process and finished products quality control test for tablet and capsules according to pharmacopoeias. *Asian J Pharm Res Dev*, 2018; 6: 60-68.[DOI]
- [27] Sopyan I, Wahyuningrum R, Sunan KSI. An Experimental Design in the optimization of various tablet excipient formulations: a concise review. *Int J Appl Pharm*, 2022; 14: 28-32.[DOI]
- [28] Reddy S, Bhavanam P, Lekkala V et al. Formulation and evaluation of fenofibrate tablets using different binding agents. *Int J Innov Pharm Res*, 2010; 1: 33-36.
- [29] Nisha G, Chellappan DK, Tambuwala MM et al. Oral nanoemulsion of fenofibrate: formulation, characterization, and in vitro drug release studies. *Assay Drug Dev Techn*, 2021; 19: 246-261.[DOI]
- [30] Mohanty S, Sahoo S, Patra S et al. Design and development of fenofibrate solid for solubility enhancement. *Curr Trends Biotechnol Pharm*, 2023; 17: 671-681.
- [31] Salama FMM, Nassar MWI, Sharaf El-Din MMK et al. Determination of fenofibrate and the degradation product using simultaneous UV-derivative spectrometric method. *Am J Anal Chem*, 2011; 2: 332-343.[DOI]
- [32] Lynnerup JT, Eriksen JB, Bauer-Brandl A et al. Insight into the mechanism behind oral bioavailability-enhancement by nanosuspensions through combined dissolution/permeation studies. *Eur J Pharm Sci*, 2023; 184: 106417.[DOI]
- [33] Komsta L, Misztal G. Determination of fenofibrate and gemfibrozil in pharmaceuticals by densitometric and videodensitometric thin-layer chromatography. *J AOAC Int*, 2005; 88: 1517-1524.