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Original Article

FORMULATION AND CHARACTERIZATION OF HPMC AND HPMCAS BASED SOLID DISPERSIONS OF FENOFIBRATE: A COMPARATIVE STUDY

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ABSTRACT

Objective: The aim of the present study was to investigate the effect of novel polymeric carriers and to develop solid dispersion formulation that could improve *in vitro* profile of Fenofibrate (FB).

Methods: Spray drying technique was used to fabricate solid dispersions with hydrophilic carriers, mainly hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS). Solid dispersions in the form of spray-dried powder were characterized with respect to the pure drug and the corresponding physical mixtures by optical microscopy, x-ray diffraction (XRD), fourier transform infrared (FT-IR) spectroscopy and differential scanning calorimetry (DSC). Size and morphology of optimized solid dispersion were performed by scanning electron microscopy (SEM). Furthermore, *in vitro* dissolution comparisons were carried out between the optimized solid dispersion against the pure drug and the physical mixtures.

Results: Solubility studies demonstrated that the solubility of FB was not affected by pH change. The transformation of crystalline FB into an amorphous solid dispersion powder has been clearly demonstrated by optical microscopy. The molecular dispersion of drug in the dispersion matrix prepared by spray drying was confirmed in XRD and DSC studies. IR spectroscopy was observed with negligible incompatibility of the drug with polymers. Spherical morphology was observed in SEM with no evidence of FB crystals. The prepared solid dispersions exhibited dissolution improvement as compared to the pure drug and spray dried FB in 0.05 M SLS, with HPMCAS as the superior carrier over HPMC.

Conclusion: The present study vouches better *in vitro* profile of FB from spray-dried HPMCAS based solid dispersions.

Keywords: Solubility, HPMC, HPMCAS, Solid dispersions, Crystallinity

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INTRODUCTION

About 40% of New Chemical Entities in drug development pipelines suffered from poor water solubility or dissolution rate-limited absorption which eventually falls into the Biopharmaceutics Classification System (BCS) Class II and thus they fail to reach the market. These poorly water-soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity [1]. Techniques have been developed to address the low aqueous solubility challenges, including chemical modification, such as pro-drugs and salt formation, or formulation methods such as particle size reduction, co-crystal formation, inclusion complexes using cyclodextrins and lipid formulations and solid form changes such as nanocrystals and amorphous dispersions of API and polymers [2]. Of these techniques, amorphous solid dispersion is a useful approach to increase the dissolution rate of poorly water-soluble drugs and thereby improve their bioavailability, although this must be proved for each drug. The preparation of the solid dispersion involves drug deposition on the surface of an inert carrier which results in a greater surface area of the drug leading to a faster rate of dissolution [3]. Recently used methods for the preparation of amorphous solid dispersions include mechanical grinding, melting, hot melt extrusion, spray drying, lyophilization and supercritical fluid precipitation [4]. Spray drying is one of the effective methods for preparing amorphous solid dispersion which consists of suspending the drug and the polymer in a common solvent and then drying it to form uniform nanoparticulate size powder [5]. The scalability and efficient critical process parameters of spray drying technology based solid dispersions are widely applied in the pharmaceutical industry, which provides equalized content uniformity and nanosized distributed solid surfaces.

FB, a prodrug of fenofibric acid, is used for the treatment of hypertriglyceridemia, mixed dyslipidemia, and hyper-cholesterolemia, as it can reduce levels of triglycerides, total cholesterol and low-density lipoprotein [6]. However, FB is a neutral lipophilic drug (log P = 5.2), which is practically insoluble in water. It is classified as a class II BCS drug and oral bioavailability of approximately 30% is reported in humans. Many nanoformulations like mesoporous solid particles, liposomes or tablet approaches have been studied to improve the solubility of FB. However, the majority of these formulations used either a special matrix of mesoporous surfaces, superdisintegrants or surfactants as modified excipients lacking long-term biocompatibility or involved technically challenging processes. Some reports have confirmed that silica can act as an immunogenic sensitizer and induce contact hypersensitivity. Furthermore, the formulation must be carefully designed because the pore architecture of silica may greatly influence its biocompatibility, and high dose and long-term usage should be avoided [5, 6]. The spray drying technique used for the preparation of the solid dispersion using different hydrophilic polymers such as HPMC and HPMCAS has not been explored to improve the aqueous solubility of FB. In the present study, an attempt was made to develop and optimize a solid dispersion system using different proportions of drug per carrier. Furthermore, the present study aims to clarify the potential for improving the solubility and dissolution rate of FB using hydrophilic polymers such as HPMC and HPMCAS by spray drying technology.

MATERIALS AND METHODS

HPMCAS-LF and HPMC (K100 Grade) were obtained from signet chemicals corporation, Mumbai. FB was procured from macleod's pharmaceuticals, Mumbai. HPLC grade acetonitrile, hydrochloric acid (HCl), and dichloromethane were purchased from SD fine chemicals llimited, India. Methanol and potassium dihydrogen phosphate were purchased from rankem India. Phosphoric acid was purchased from fischer scientific limited, India. All chemicals and reagents utilized were of analytical grade. Triple distilled water (Rions, India) was used throughout the entire study.

High-performance liquid chromatography (HPLC) analysis of FB

Reversed-phase column based high-performance liquid chromatographic method (Nexera X2, Shimadzu, Japan) was used for quantification of FB in analytical media. The LC system consisted of a

pump configured to Lab Solutions software with auto-injecting facility. The HPLC was equipped with a column oven and the analytical column used was Enable C-18; 4.6 mm × 250 mm; 5 µm in diameter with an injection loop of 20 µl. The mobile phase used was acetonitrile and acidified water (pH of water adjusted with phosphoric acid to 2.5±0.1) (70:30) at a flow rate of 1 ml/min. The injection volume was 5 µl with a run time of 20 min and the drug peak was observed at 286 nm through photodiode array (PDA) detector. Column equilibration was done at least 30 min prior to the injection of the drug solution [7].

Solubility determination in different media

Equilibrium solubility of FB was determined at 37±1 °C under physiological pH conditions i.e. 0.1 N HCl, phosphate buffer (PB) pH 4.5, pH 6.8 and in different media such as distilled water and sodium lauryl sulphate (SLS) 25 mmol and 0.05M using validated shake flask method [8]. An excess amount of drug i.e. 10 mg of FB was added to glass vials containing 5 ml of each medium and allowed to equilibrate for 24 h. The content of each vial was filtered through a 0.22 µm membrane filter (Millipore, India) and was analyzed using HPLC.

Preparation of binary systems

Preparation of HPMC and HPMCAS physical mixtures of FB

For the preparation of physical mixtures, FB and polymers were added in different ratios (2:1, 1:1 and 1:2) and were mixed thoroughly with the help of pestle-mortar to obtain homogeneous mixtures (table 1). The resulting mixture was passed through sieve #40 and was stored in a desiccator until use [9].

Preparation of spray dried FB and solid dispersions of FB with HPMC and HPMCAS

Spray dried FB was prepared to check if the process i.e. spray drying has any effect on the crystallinity of pure drug. FB was dissolved in methanol to form a 2% *w/v* solution. This solution was sonicated for 5 min. to obtain a clear solution. It was subjected to spray drying (Lab Ultima, LU 228 Advanced, Mumbai), keeping the inlet temperature at 50 °C; outlet temperature 40 °C; feed pump flow rate 3 ml/min; aspirator speed 65 m^3/h, a vacuum of 90 mm/Hg and atomization pressure at 1.2 kg/cm^2. Solid dispersions of FB were also prepared in the following compositions by spray drying using the above-mentioned conditions (table 1) [9].

Table 1: Physical mixtures and spray dried solid dispersions composition

		Spray dried solid dispersions composition	
FB: HPMC	**Ratio**	**FB: HPMC**	**Ratio**
PMC1	2:1	SD MC1	2:1
PMC2	1:1	SD MC2	1:1
PMC3	1:2	SD MC3	1:2
FB: HPMCAS		**FB: HPMCAS**	
PM CAS4	2:1	SD CAS4	2:1
PM CAS5	1:1	SD CAS5	1:1
PM CAS6	1:2	SD CAS6	1:2

Characterizations of physical mixtures and solid dispersions

Optical and polarized microscopy

Each sample (<0.1 mg) was mounted on a glass slide with a brush, covered with silicone oil and a coverslip and was observed under the microscope (Lecia DMLP, Germany). Light intensity was adjusted and observations were done under normal and polarized light (by engaging the polarizer). Birefringence patterns were observed at a high-resolution scale and images were acquired.

FT-IR spectroscopic analysis

FT-IR Spectrograms were obtained using FT-IR spectrometer (Perkin Elmer, USA) by the conventional KBr pellet method [9]. The samples were grounded gently with anhydrous KBr and compressed to form pellets and the scanning was carried out in a range of 4000-400 cm^{-1}.

DSC analysis

Each sample (2 mg) was scanned in an aluminum pan over the range of 20 °C to 220 °C, at a rate of 10 °C/min under the controlled environment of liquid nitrogen at a rate of 50 ml/min. Thermal data analysis of the DSC thermograms was conducted using TA Universal Analysis (DSC Q 20-2661 TA Instruments, USA).

XRD analysis

XRD measurements were performed using X-ray diffractometer (X'PERT PRO, PANalytical, Netherlands). Samples were irradiated with monochromatic Cu radiation and patterns were obtained by continuous scanning at a step size of 0.017 °, with detector resolution in 2θ (diffraction angle) between 3.5 ° to 50 θ. The generator settings used were 40 mA and intensity resolution of 45kV at ambient temperature [10].

Scanning electron microscopy

The electron microscopy analysis was carried out to study the surface morphology of optimized dispersions in a scanning electron microscope (Carl Zeiss SUPRA 55). Samples were gold coated and mounted on the stubs using double-sided carbon adhesive tape and were analyzed in different magnification scales at 100 kV ionizing radiations [11].

***In vitro* dissolution studies**

FB, spray dried FB, physical mixtures and solid dispersions equivalent to 54 mg of drug were subjected to *in vitro* dissolution testing using USP Type II (Paddle type) Dissolution Apparatus (Electrolab TDT-08l Dissolution Tester, India), using 900 ml of 0.05M SLS as dissolution medium. The rotation speed of paddle was kept at 50 rpm and the temperature was set at 37±2 °C. Samples (5 ml) were withdrawn at intervals of 5, 10, 15, 30, 45, 60, 90, 120 min. and were replaced with an equal amount of dissolution medium to reimburse the loss during sampling After each withdrawal, aliquots were filtered through a 0.2 µm membrane filter (Millipore, India) and analyzed using optimized HPLC method [10, 11].

Calculation of dissolution parameters

Percent Dissolution Efficiency (DE) for each formulation was computed as the percent ratio of an area under the dissolution curve up to the time, t, to that of the area of the rectangle described by 100% dissolution at the same time and was calculated by using equation 1

$$DE = \left(\frac{\int_0^t y.dt}{y100.t}\right) 100 \text{ - - - - - - - - - - - - - } 1$$

Where y is the percent drug dissolved at time t. For these formulations, DE_{30} and DE_{60} were calculated. Other dissolution parameters such as t_{60}, DP_5, DP_{30}, and DP_{120} were also calculated (t_{60} is the time taken to release 60% of the drug and DP is the percent drug released at a particular time).

RESULTS AND DISCUSSION

Solubility determination in different media

Results from saturation solubility studies demonstrated that there was no significant difference between saturation solubility values of

FB at different pH. This is attributed to the fact that it has no ionizable group, so its solubility is not influenced by a change in pH. The solubility of FB increased significantly in 25 mmol SLS and 0.05 M SLS solutions which might be attributed to its micellar solubilization property [12]. The solubility data in various media are given in fig. 1.

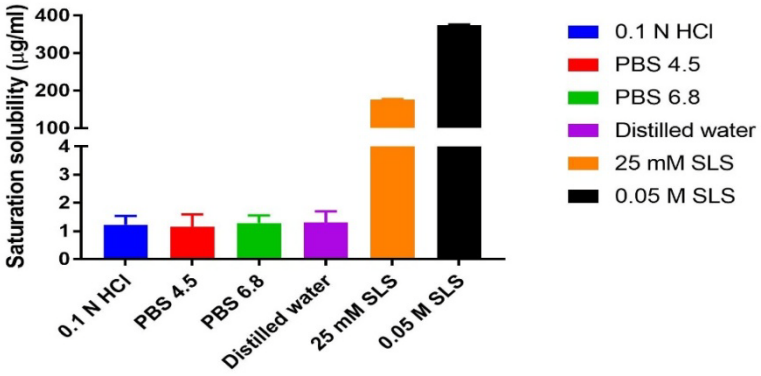
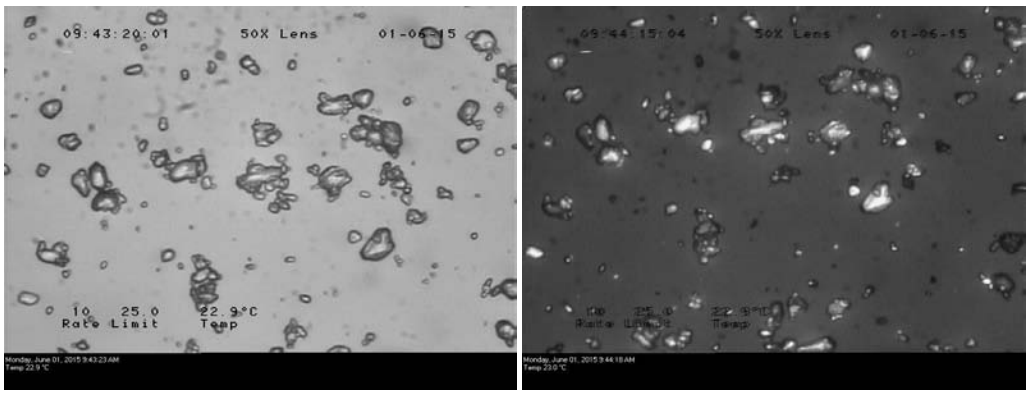
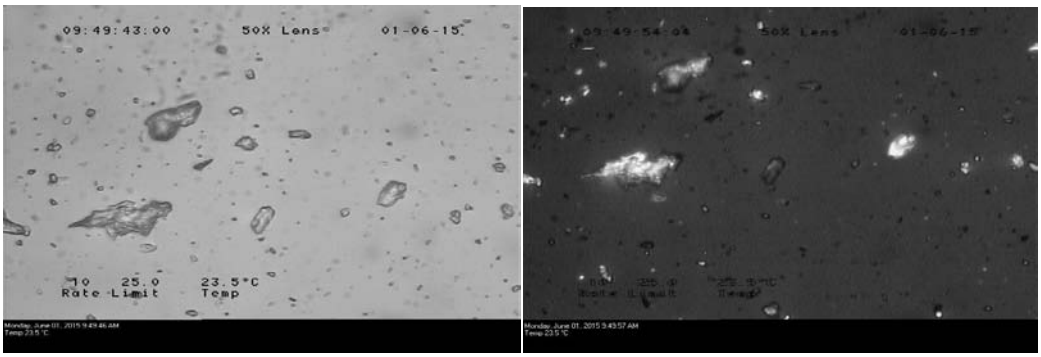


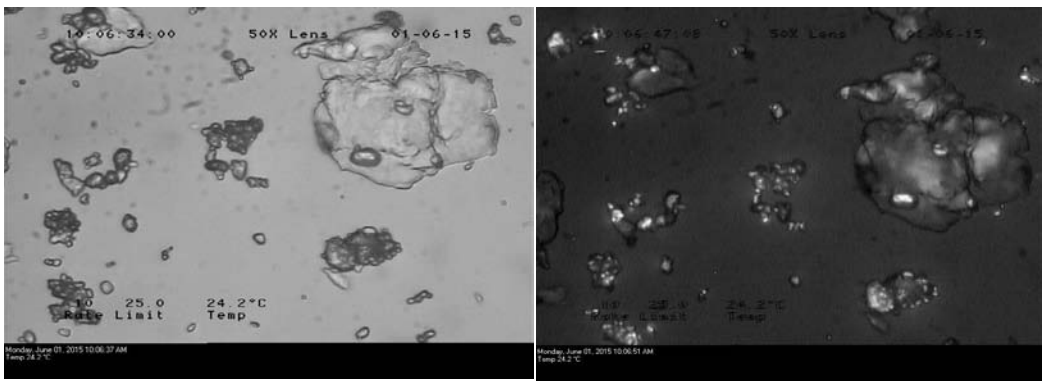
Fig. 1: Saturation solubility of FB in different media (mean±SD, n=3)



(a1) **(a2)**



(b1) **(b2)**



(c1) **(c2)**

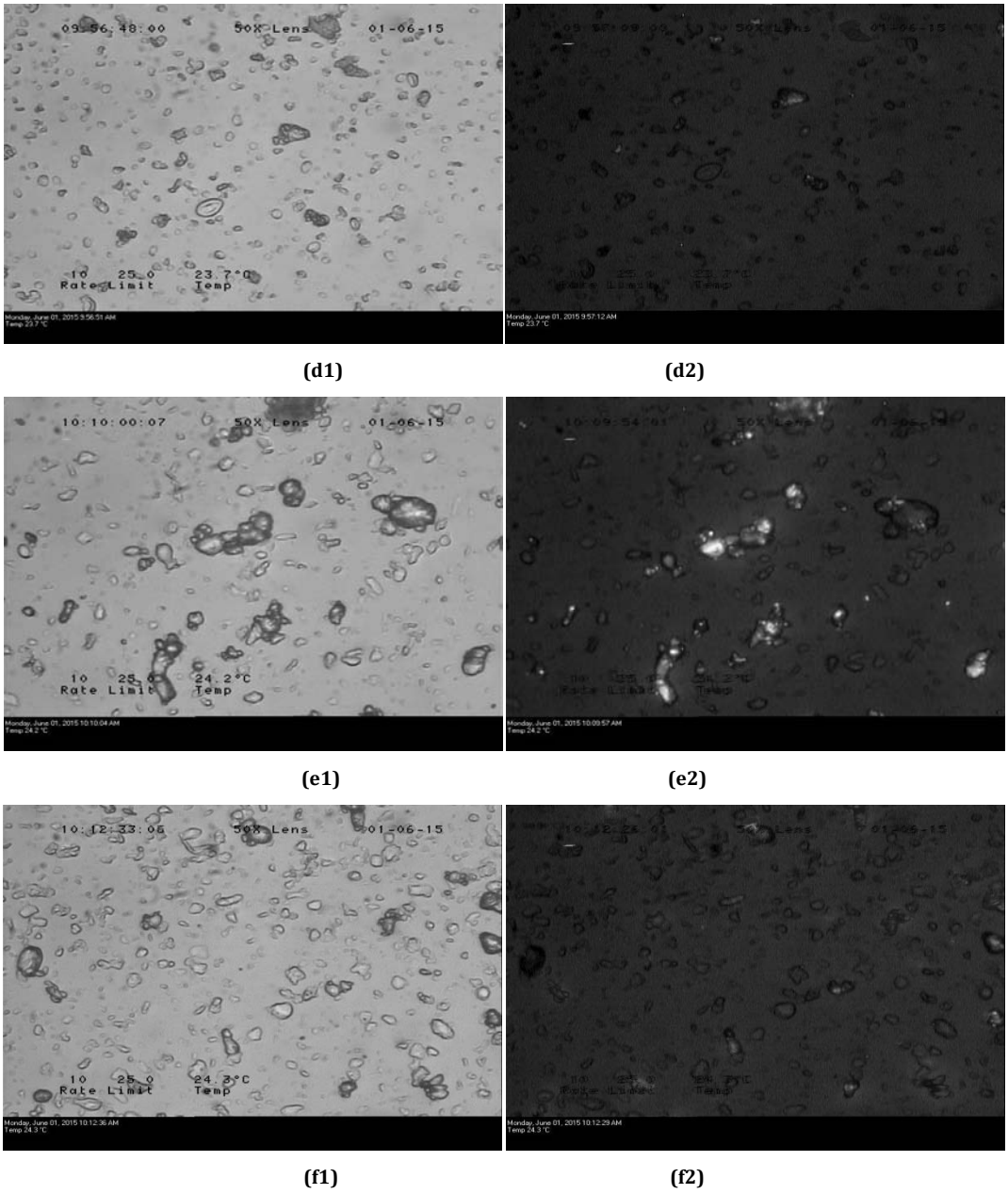


Fig. 2: Optical micrographs of (a1) FB (b1) Spray-dried FB (c1) HPMC physical mixture (d1) HPMC solid dispersion (e1) HPMCAS physical mixture (f1) HPMCAS solid dispersion. Polarized micrographs of (a2) FB (b2) Spray-dried FB (c2) HPMC physical mixture (d2) HPMC solid dispersion (e2) HPMCAS physical mixture (f2) HPMCAS solid dispersion

Characterizations of FB, spray dried FB, HPMC, HPMCAS, physical mixtures and solid dispersions

Optical and polarized microscopy

Optical and polarized microscopy was done to observe the birefringence pattern. Fig. 2 showed optical and polarized micrographs of the drug, polymeric carriers, physical mixtures and solid dispersions. Presence of birefringence confirms the presence of crystallinity in the samples. However, loss of crystallinity was observed in prepared physical mixtures and solid dispersions by uniform dispersion of the drug in molecular matrix. This phenomenon suggested effective encapsulation of FB into the hydrophilic matrix of HPMC and HPMCAS with no evidence of FB crystals on the surface.

FT-IR spectroscopic analysis

The IR spectrum provides information about the chemical bonds, characteristics functional group and usually detects interactions between drug and carrier in the solid dispersion. The spectrum overlay plot of the drug, polymers, physical mixtures and optimized solid dispersions are depicted in fig. 3. The IR spectrum of the drug showed major peaks at various C-H stretches from 2872 cm^{-1} to 3068 cm^{-1}. The C=C stretches were observed at 1594 cm^{-1} and the bands at 1173 cm^{-1} and 1291 cm^{-1} were attributed to C-O stretches. The spectra for the raw and spray-dried drug were similar, confirming that the drug did not undergo any transformation after spray drying [5]. The IR spectra of the solid dispersion and the physical mixture of the drug with HPMC and HPMCAS clearly showed that there is no incompatibility of the drug with the polymer. No significant shifts were observed in the IR spectrum of the solid dispersion and all the stretching as well as bending vibrations such as OH stretch, C-H stretches, C-O stretch, C=C stretch, C-H bending, C-Cl stretches were observed. These findings observed negligible chemical interaction between drug and polymers and successfully be transformed into an effective pharmaceutical dosage form.

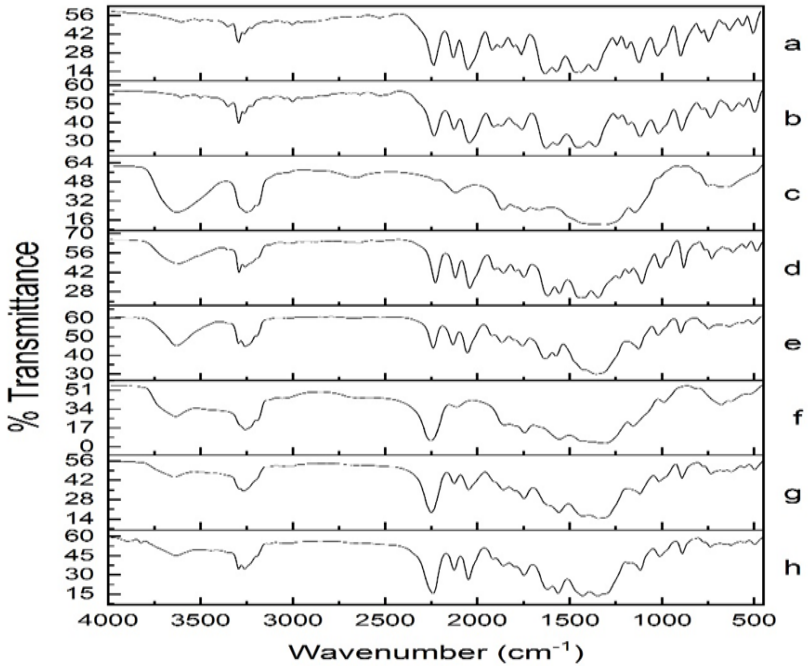


Fig. 3: FT-IR spectrographs of (a) FB (b) Spray dried FB (c) HPMC (d) HPMC physical mixture (e) HPMC solid dispersion (f) HPMCAS (g) HPMCAS Physical Mixture (h) HPMCAS solid dispersion

DSC analysis

Melting endotherms of FB and spray dried FB were observed at around 81.56 °C and 82.24 °C, respectively, confirming its crystalline state with no major effect of spray drying on endotherm shifting. Glass transition temperature of HPMC and HPMCAS were observed at around 170 °C and 120 °C, respectively. The physical mixtures of FB with different polymers, with the melting endotherms at 82.23 °C and 81.63 °C, confirmed the residual crystallinity due to the homogenous mixture formed (fig. 4). Furthermore, broad endothermic peaks in these mixtures could be attributed to the absence of endothermic relaxation [13]. Solid dispersions presented with no incidence of crystallinity, indicating perfect miscibility of drug and polymer to form stable solid dispersion for oral delivery [14].

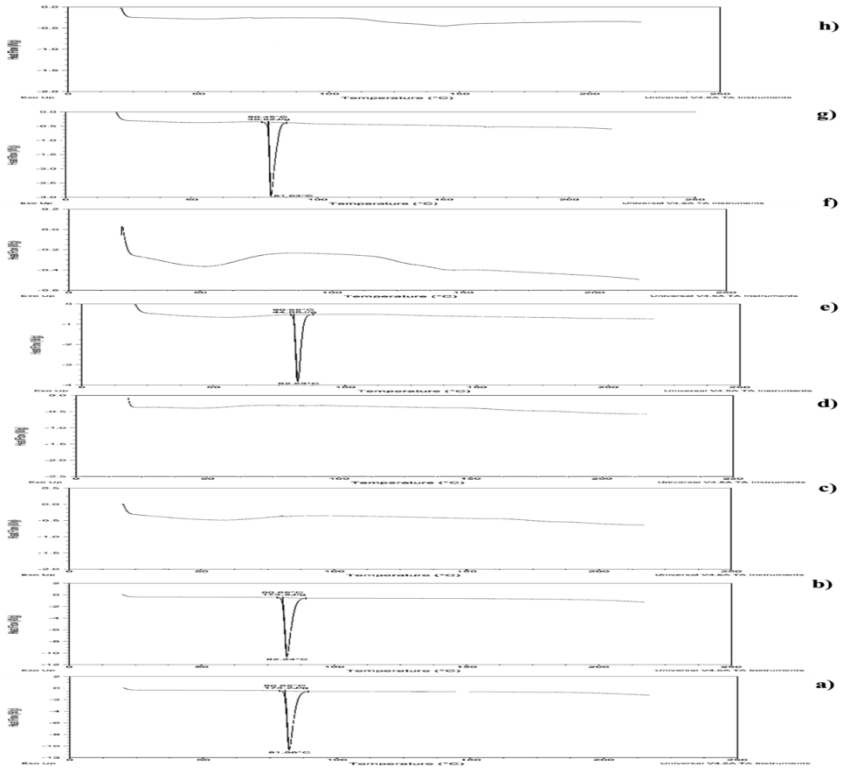


Fig. 4: DSC thermograms of (a) FB (b) Spray-dried FB (c) HPMC (d) HPMC physical mixture (e) HPMC solid dispersion (f) HPMCAS (g) HPMCAS Physical Mixture (h) HPMCAS solid dispersion

XRD analysis

In the XRD of FB and spray-dried FB, sharp peaks were observed at a diffraction angle (2θ) of 12.03 °, 14.49 °, 15.81 °, 16.31 °, 16.77 °, 17.97 °, 19.37 °, 20.68 °, 20.94 °, 21.71 °, 21.89 ° and 22.33 °, indicating its crystalline nature and reduction of crystallinity was observed in spray-dried drug [15]. Partial amorphization was observed in the physical mixture, whereas, optimized solid dispersions observed with a reduction in the crystallinity index with an absence of diffraction patters indicating a change in overall geometry of crystalline to amorphous form and suggesting effective molecular dispersion of FB in solid dispersion formulation (fig. 5).

This phenomenon may be attributed to the attainment of molecular dispersion state in these formulations and confirmed the amorphous transformation of drug FB in the solid dispersions [15].

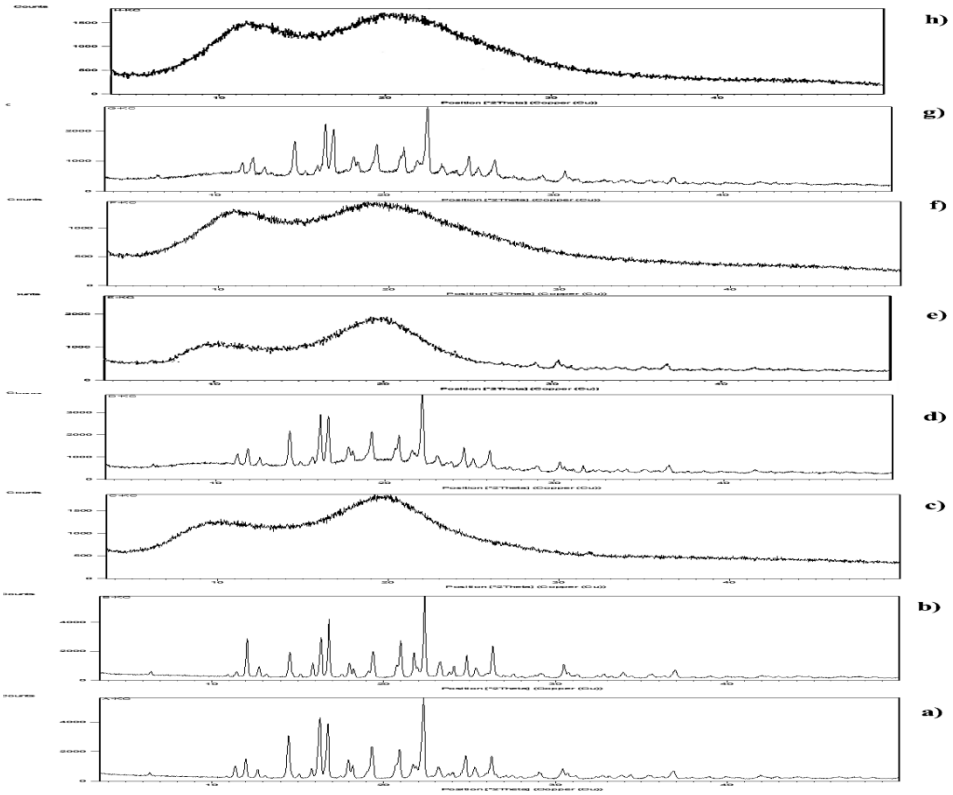
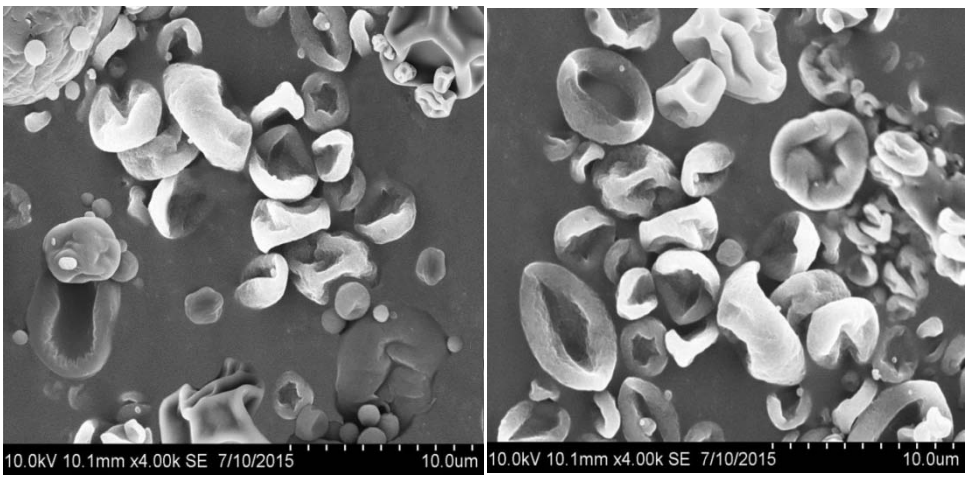


Fig. 5 (a): XRD patterns of (a) FB (b) spray-dried FB (c) HPMC (d) HPMC physical mixture (e) HPMC solid dispersion (f) HPMCAS (g) HPMCAS physical mixture (h) HPMCAS solid dispersion

Scanning electron microscopy

The particles of amorphous dispersions in SEM seemed to be collapsed and spherical in shape due to the rapid evaporation of solvent during spray drying (fig. 6). The size and morphology of spray dried amorphous solid dispersions confirms a similar surface state for solid dispersions of both the polymers, negotiating the effect of surface state on the dissolution rate [16].



(a) **(b)**

Fig. 6: SEM of (a) HPMC solid dispersion (b) HPMCAS solid dispersion

In vitro dissolution studies

The *in vitro* release profile of FB, physical mixtures and optimized formulation in 0.05 M SLS is shown in fig. 7 and 8, respectively. A low release rate of 16.31 % of pure drug indicated the need for enhancing the dissolution regime in order to develop a successful drug product. However, the presence of polymers significantly increased the dissolution of FB from the physical mixtures, i.e. PMC 1, PMC 2, PMC 3 containing HPMC and PM CAS 1, PM CAS 2 and PM CAS 3 containing HPMCAS. For HPMC, the rate of dissolution was found to be highest in the physical mixture PMC 3 i.e. 57.13% in 2 h. In the case of HPMCAS, the percentage cumulative drug released (%CDR) was highest in PM CAS 3 i.e. 62.84% in 2 h. This suggests that HPMCAS has a significant effect on the solubilisation of the drug as compared to HPMC in the formulation [16]. Moreover, it was observed that the dissolution of the drug from its carrier first increases and then it gets stable after some time, indicating the solubilizing effect of both the polymers [17, 18]. This enhancement of dissolution of FB from HPMCAS can be described by several factors viz. lack of crystallinity, i.e., amorphization, increased wettability and dispersibility, and particle size reduction [19-21]. Also, prevention of aggregation during dissolution and particle size reduction could also be attributed to a better dissolution profile. Overall, HPMCAS showed better augmentation in dissolution rate than HPMC and showed enhanced release rate than pure drug and marketed product.

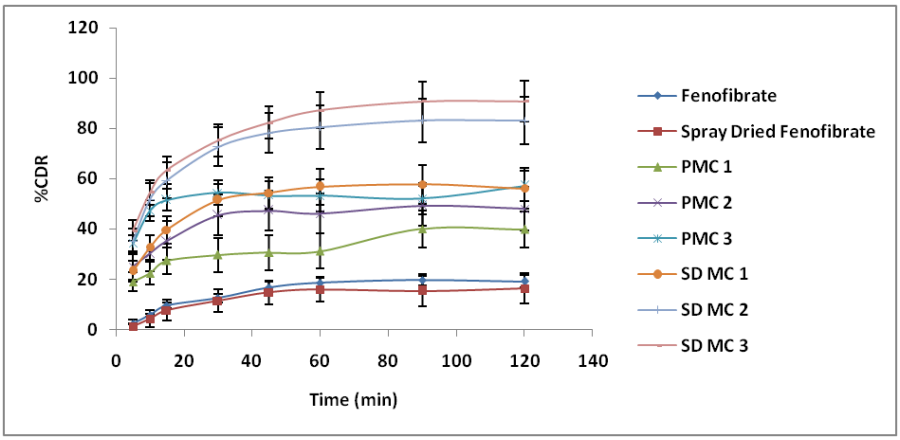


Fig. 7: Dissolution curves of FB, spray dried FB, physical mixtures and prepared solid dispersions of FB with HPMC (mean±SD, n=3) (P<0.05, compared PMC 1-PMC 3 with pure Fb) (P<0.001, compared SD MC 1-SD MC 3 with pure FB)

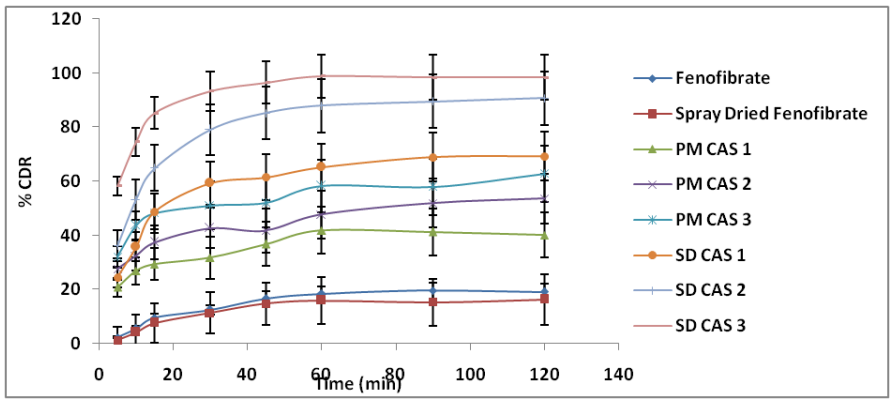


Fig. 8: Dissolution curves of FB, spray dried FB, physical mixtures and prepared solid dispersions prepared with HPMC and HPMCAS (mean±SD, n=3) (P<0.05, compared PM CAS1-PM CAS 3 with pure FB) (P<0.001, compared SD CAS 1-SD CAS 3 with pure FB)

Dissolution parameters of solid dispersions of FB with HPMC and HPMCAS

The values for various dissolution parameters calculated for six solid dispersions prepared by using the different drug to polymer ratios are shown in table 2. It was evident that HPMCAS enhanced the dissolution rate of the drug to a greater extent. HPMCAS dissolution curve shoots up quickly than HPMC dissolution curve and was better at initiation and maintenance of supersaturation. It can be seen that solid dispersions SD3 and SD6 showed best results i.e. have the highest values for DE_{60} for HPMC and HPMCAS, respectively [22].

Table 2: Dissolution parameters of solid dispersions

Solid dispersion batches	DE_{30}	DE_{60}	DP_{5}	DP_{30}	DP_{120}	t_{60}(min)
SD MC 1	39.40 %	44.83 %	23.26 %	51.48 %	56.14 %	-
SD MC 2	52.41 %	64.90 %	35.21 %	72.65 %	82.94 %	15.75
SD MC 3	55.54 %	68.66 %	39.23 %	75.29 %	90.82 %	13.14
SD CAS 1	41.14 %	51.49 %	24.52 %	59.27 %	69.24 %	34.98
SD CAS 2	56.32 %	70.33 %	36.12 %	79.09 %	90.72 %	12.87
SD CAS 3	73.81 %	85.01 %	58.26 %	93.23 %	98.37 %	5.54

CONCLUSION

We focused on the comparison of HPMC and HPMCAS as the versatile hydrophilic polymers for the attainment of amorphization and enhancement of *in vitro* dissolution. The formed solid dispersion was in the amorphized state in the solid state characterizations and revealed highest in the release, particularly with HPMCAS based solid dispersion. Multi-folds augmentation in release behavior of optimized solid dispersions prepared with HPMCAS was observed and was statistically significant ($p<0.05$) as compared with the pure API. These studies revealed that even though the drug remains in amorphous form in solid dispersions based on both the polymers, HPMCAS based amorphous solid dispersions demonstrated improved dissolution profile as compared to HPMC based dispersions.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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