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Solid dispersions of fenofibrate: Comparision of natural and synthetic carriers

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Abstract
The main objective of the study was to compare the effect of natural carriers and synthetic carriers in dissolution of fenofibrate (BCS class II), poorly soluble drug. Fenofibrate is an anti hyperlipidemic drug which reduces both cholesterol and triglycerides in the blood. Nowadays the formulation of poorly soluble compounds for oral delivery is the most frequent and greatest challenge to formulation scientists in pharmaceutical industry. There are many drugs for which dissolution poses a challenge for formulating oral dosage forms leading to bioavailability problems. To improve solubility of the drug, solid dispersions were prepared by different methods like physical mixture and kneading method with natural and synthetic carriers like agar, karaya gum, treated agar, modified karaya gum, PEG 4000 and PEG 6000 in the ratios of 1:2 to 1:10. Resultant formulations were evaluated for solubility, assay, flow properties, FTIR, X-ray diffraction, DSC and *in vitro* dissolution. Solubility of the solid dispersions was enhanced when compared to pure drug solubility (0.018 mg/ml). Natural gums, agar and karaya gum were modified and the swelling nature and viscosity of treated agar and modified karaya gum were less. Formulations with modified gums as carriers showed fast release (treated agar 87.56±1.40% release by K10 and modified karaya gum 93.73±1.35% release by K20) when compared to agar (79.46±1.37% release by K5) and karaya gum (82.16±1.37 % release by K15). When compared to natural carriers, synthetic carriers PEG 4000 (101.83±1.14% release in 60 mins by K25) and PEG 6000 (101.19±1.12% release in 30 minutes by K30) showed greater release. When compared to solid dispersions by physical mixture, kneading method formulations showed fast release. FTIR studies confirmed that there is no interaction between the drug and excipients. The solid state characterization of solid dispersion formulation by XRD and DSC studies confirmed that the drug present in the formulation was in an amorphous state. The optimized formulation was subjected to stability studies and was found to be stable. Hence, it can be concluded that solid dispersions of fenofibrate prepared by kneading method with synthetic carrier PEG 6000 are better in enhancing the dissolution rate.

Keywords: Fenofibrate, modified karaya gum, polyethylene glycol 4000, polyethylene glycol 6000

Introduction
Over the past two decades, there has been an increased research for novel drug delivery systems (NDDS) to improve safety, efficacy and patient compliance. The discovery and development of a new chemical entity (NEC) is highly expensive and time consuming affair. Hence the pharmaceutical industries are focusing on the design and development of new drug delivery systems for the existing drugs, leading to improved bioavailability, reduced adverse effects and more patient compliance [1]. Oral bioavailability of drugs depends on its dissolution rate, therefore major problems associated with these drugs are, its low aqueous solubility, which results in poor bioavailability after oral administration. Solubility of drug candidates may be altered by modifying the crystal form or by changing solvent properties and conditions. It may also be altered by altering the chemical composition, as seen with salt formation, co-crystals and solid complexes [2]. Another means of improving "apparent solubility" is by converting the crystalline drug into an amorphous state. An amorphous phase has higher free energy, enthalpy and entropy than the crystalline counterpart and thus finds application in improving oral bioavailability for biopharmaceutical classification (BCS) class II or class IV compounds [3]. Various techniques have been used in attempt to improve the solubility and dissolution rates of poorly water soluble drugs, which include solid dispersion, micronization, lipid based formulations, melt granulation, direct compaction, solvent evaporation, co-precipitation, adsorption, ordered mixing, liquid-solid compacts, solvent deposition and inclusion complexation [4]. In these techniques carrier is important in improving the solubility and dissolution rate. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs [5]. Solid dispersion consists

of a hydrophobic drug dispersed in hydrophilic matrix [6]. In solid dispersions, molecular dispersions represent particle size reduction, after carrier dissolution the drug is molecularly dispersed in dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of poorly water soluble drug and highly soluble carriers [7]. If higher surface area is formed, it results in enhanced dissolution rate and bioavailability [8]. The drug solubility is mainly related to drug wettability to enhance the dissolution in solid dispersions, even without any surface activity also observed such as urea [9]. Anyhow carriers will influence the dissolution rate by co-solvents effect and direct dissolution particles shown in solid dispersion particles, show a high degree of porosity. Increase in porosity also depends on carrier properties, more porous particles result in higher dissolution rate [10]. Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [11]. Solid dispersions can be prepared by fusion method, solvent evaporation**,** spray-drying**,** lyophilization technique, melt evaporation, melt extrusion method, melt agglomeration process, use of surfactant, kneading technique, electrospinning method and super critical fluid (SCF) technology [1, 3, 5]. Fenofibrate widely prescribed anti-hyperlipidemic drug belongs to class II under BCS and exhibits variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability [12]. The hydrophilic carriers such as gums of natural origin like agar and karaya gum in modified form and synthetic carriers polyethylene glycol (PEG) 4000 and PEG 6000, are selected which helps in enhancing the solubility of the drug. The present study is an attempt to overcome the poor aqueous solubility of fenofibrate, by solid dispersions using various techniques such as physical mixture and kneading method. The prepared solid dispersions will be subjected to physicochemical characterization and *in vitro* studies.

Materials and Methods

Fenofibrate was obtained as gift sample from Suven life sciences, hyderabad. Karayagum and agar were purchased from Yarrow chem products, Mumbai. Poly ethylene gycol (PEG) 4000, PEG 6000 and Sodium lauryl sulphate were purchased from SD fine chemicals limited.

Preparation of solid dispersions

a) Physical mixture method (PM)

The physical mixtures (PM) of drug with different carriers in ratios of 1:2 to 1:10 were prepared by blending method. The blended mixture was passed through sieve # 60 and the resultant solid dispersion was further evaluated. Formulations of physical mixture are given in table 1.

Table 1: Formulations of physical mixture of fenofibrate and carriers

Formulation Code	Drug (mg)	Carriers					
		Agar (mg)	Treated agar (mg)	Karaya gum (mg)	Modified karaya gum (mg)	PEG 4000 (mg)	PEG 6000 (mg)
F1	200	400	-	-	-	-	-
F2	200	800	-	-	-	-	-
F3	200	1200	-	-	-	-	-
F4	200	1600	-	-	-	-	-
F5	200	2000	-	-	-	-	-
F6	200	-	400	-	-	-	-
F7	200	-	800	-	-	-	-
F8	200	-	1200	-	-	-	-
F9	200	-	1600	-	-	-	-
F10	200	-	2000	-	-	-	-
F11	200	-	-	400	-	-	-
F12	200	-	-	800	-	-	-
F13	200	-	-	1200	-	-	-
F14	200	-	-	1600	-	-	-
F15	200	-	-	2000	-	-	-
F16	200	-	-	-	400	-	-
F17	200	-	-	-	800	-	-
F18	200	-	-	-	1200	-	-
F19	200	-	-	-	1600	-	-
F20	200	-	-	-	2000	-	-
F21	200	-	-	-	-	400	-
F22	200	-	-	-	-	800	-
F23	200	-	-	-	-	1200	-
F24	200	-	-	-	-	1600	-
F25	200	-	-	-	-	2000	-
F26	200	-	-	-	-	-	400
F27	200	-	-	-	-	-	800
F28	200	-	-	-	-	-	1200
F29	200	-	-	-	-	-	1600
F30	200	-	-	-	-	-	2000

b) Preparation of solid dispersion by kneading method (KM): The solid dispersions of the drug were prepared with various carriers at various drug to carrier ratios of 1:2 to 1:10 (as given in Table 2), by kneading method using mortar and

pestle (glass). The drug and carrier were mixed; methanol was added in small quantity and triturated vigorously until damp granular mass was obtained. The mixture was then dried in hot air oven at 45°C to form dry granules. Then the mixture was taken and passed through sieve #60 and the granules were retained and further evaluated.

Table 2: Formulations of solid dispersions of fenofibrate and carriers by kneading method

Formulation Code	Drug (mg)	Carriers					
		Agar (mg)	Treated agar (mg)	Karaya gum (mg)	Modified karaya gum (mg)	PEG 4000 (mg)	PEG 6000 (mg)
K1	200	400	-	-	-	-	-
K2	200	800	-	-	-	-	-
K3	200	1200	-	-	-	-	-
K4	200	1600	-	-	-	-	-
K5	200	2000	-	-	-	-	-
K6	200	-	400	-	-	-	-
K7	200	-	800	-	-	-	-
K8	200	-	1200	-	-	-	-
K9	200	-	1600	-	-	-	-
K10	200	-	2000	-	-	-	-
K11	200	-	-	400	-	-	-
K12	200	-	-	800	-	-	-
K13	200	-	-	1200	-	-	-
K14	200	-	-	1600	-	-	-
K15	200	-	-	2000	-	-	-
K16	200	-	-	-	400	-	-
K17	200	-	-	-	800	-	-
K18	200	-	-	-	1200	-	-
K19	200	-	-	-	1600	-	-
K20	200	-	-	-	2000	-	-
K21	200	-	-	-	-	400	-
K22	200	-	-	-	-	800	-
K23	200	-	-	-	-	1200	-
K24	200	-	-	-	-	1600	-
K25	200	-	-	-	-	2000	-
K26	200	-	-	-	-	-	400
K27	200	-	-	-	-	-	800
K28	200	-	-	-	-	-	1200
K29	200	-	-	-	-	-	1600
K30	200	-	-	-	-	-	2000

Modification of natural carriers

a. Karaya gum: The tears of Karaya gum were pulverized and then passed through sieve #100. 10 grams of the powdered gum was taken in a china dish and subjected to heating at 120°C for 2 hrs in a hot air oven [13].

b. Agar: Modified agar was prepared by suspending 5g of agar in 100ml of distilled water. The suspension was stirred at 500rpm using magnetic stirrer for 24hr. Obtained swollen masses was spread out on enameled trays and dried at room temperature for 72hr. The dried product was scrapped out and crushed in a glass pestle mortar to obtain coarse, free flowing and heterogenous particles of treated agar. It was then passed through sieve no.100.

Evaluation of modified karaya gum (MKG) and treated agar (TA): The prepared modified Karaya gum (MKG) and treated Agar (TA) was evaluated and compared with Karaya gum and Agar for the parameters, swelling index and viscosity [14].

a. Swelling index: The swelling index of the gum was measured by taking 1 gm of the gum in a 100 ml measuring cylinder and the volume was made up to 100 ml with distilled water. The initial volume occupied by the gum was noted as V_0. The measuring cylinder was stoppered and kept aside for 24 hrs. The volume to which the gum has swollen was noted as V_1.

$$\text{Swelling index} = \frac{V1 - V0}{V0} X100$$

b. Viscosity: Viscosity of the gum was measured by using Brookfield viscometer LVDV-II+Pro (Brookfield Engineering Laboratories, U.S.A). 1 gm of the gum was taken in a beaker and it was dispersed in 100 ml distilled water. The dispersion was stirred continuously for 24 hrs on a magnetic stirrer to make it homogenous. The viscosity of the dispersion was measured in centipoises (cps).

Assay: Accurately weighed amounts of solid dispersions sample equivalent to 50 mg of drug was weighed and transferred into a 100 ml volumetric flask, 20 ml methanol was added and shaken for 20 min to dissolve the drug. The volume was made to 100 ml with 0.05 M SLS in distilled water. The dispersions were filtered and 1 ml aliquot of the above solutions were taken and diluted to 10 ml with 0.05M SLS in distilled water. The absorbance of these solutions was determined at 287 nm against the blank as 0.05 M SLS in distilled water using UV-double beam Spectrophotometer [3].

Solubility studies: An excess of pure fenofibrate drug and prepared solid dispersions were added to screw capped bottles containing distilled water. Bottles are shaken mechanically

inside an orbital shaker bath at room temperature for 24hrs [3]. Then the samples were filtered using 0.45µm whatman filter paper, suitable diluted and analyzed by UV-double beam spectrophotometer at 287 nm.

Percentage practical yield: The prepared solid dispersions were weighed accurately and it was taken as theoretical yield. Then the percentage practical yield was calculated by using the formula as follows: % of practical

$$\text{yield} = \frac{\text{practical yield}}{\text{theoretical yield}} x100$$

Pre compression parameters: The prepared solid dispersions were evaluated for flowability and compressibility by angle of repose, Carr's index and Hausner's ratio.

Angle of repose: This is the maximum angle possible between the surface pile of powder and horizontal plane. Angle of repose is calculated by the following formula. $\Theta = \text{Tan}^{-1}$ (h/r)

Bulk density: Bulk density is defined as a mass of powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula. *b=M/V*

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula. *t=M/Vt

Carr's index: The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the

$$\text{Formula, C.I (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio: Hausner's ratio is an index of ease of powder flow. It was calculated by the using the formula, Hausner's ratio=*t/*d; Where *t=tapped density, *d=bulk density.

***In vitro* dissolution studies:** Dissolution studies were performed with solid dispersions prepared by different methods using USP dissolution apparatus II (Paddle type) (Electrolab TDT-08L, Mumbai). The dissolution test was performed using 900 ml of 0.05 M Sodium lauryl sulphate in water at 37±0.5˚C. The speed of rotation of paddle was set at 75 rpm. 5 ml samples were withdrawn at time points of 5, 10, 15, 20, 30, 45, 60 min and same volume was replaced with fresh media. Absorbance of solution was checked by UV-double beam spectrophotometer, (Chemito 2600), at 287 nm and drug release was determined [12].

Drug-excipient compatability studies

Fourier transformer infrared spectroscopy (FTIR): The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of solid dispersions was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu corporation (model – 8400S koyto, Japan). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure [15]. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in compound.

Differential scanning calorimetry (DSC): The physical nature of the drug, polymer and optimized formulations were studied by DSC. DSC analysis was performed using Shimazdu DSC-60 differential scanning calorimeter (DSC). The instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pin hole. Thermograms were obtained by heating the sample at a constant rate of 10°C/ min. A dry purge of nitrogen gas (50 ml/min) was used for all runs. Samples were heated from 0˚C to 350˚C. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak were noted [16].

X-Ray diffraction analysis (XRD): The crystallinity of the drug, polymer and optimized formulations were studied by XRD. The XRD analysis was performed using Shimadzu XRD-7000, X-Ray diffractometer using copper K α (λ=1.5406 Aº) radiation [16]. The data were recorded over a scanning 20 range of 5º to 50º at a step time of 0.045 steps/0.5sec.

Stability studies: The optimized formulation was subjected to stability studies according to ICH guidelines for period of three months. The samples were evaluated for physical appearance, assay and dissolution studies [15].

Results and Discussion

Natural carriers agar and karaya gum were modified and evaluated for swelling index and viscosity. Swelling index was calculated from mean readings of three determinations using mucilage. Swelling index of Modified karaya gum was 28.73±0.94%v/v when compared to karaya gum 72.72 ±1.25%v/v. The mucilage of treated agar showed least percentage of swelling index (26.66±0.86%v/v) than agar (61.53 ±1.90%v/v).

Viscosity of the gums was measured by using Brookfield viscometer LVDV-II+pro (spindle 62). The viscosity of modified Karaya gum was found to be less than Karaya gum. Viscosity of the gums at different RPMs is given in the table 3. The Rheograms of natural gum and modified gum, viscosity Vs RPM are given in figure 1.

Table 3: Viscosity of natural gum and modified gum

Name of the gum	RPM	Viscosity (cps)
Karaya gum	20	362±1.4
	40	354±1.29
	60	343±0.43
	80	339±0.8
	100	331±1.2

Modified karaya gum	20	224±0.11
	40	219±0.58
	60	217±0.33
	80	214±1.4
	100	209±1.4
Agar	20	324±2.12
	40	317±1.4
	60	311±1.6
	80	304±0.8
	100	293±1.2
Treated agar	20	206±0.58
	40	199±0.43
	60	191±1.42
	80	185±2.12
	100	176±0.8

Values are expressed as mean±SD, n=3

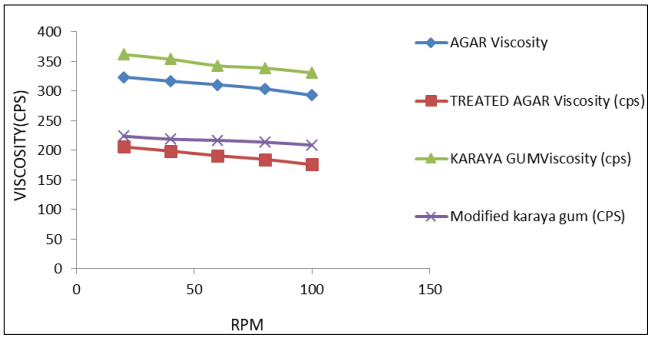

Fig 1: Rheogram of RPM vs. viscosity for natural gums and modified gums

From the table 3 & figure 1 it was observed that the viscosity of modified karaya gum and treated agar have reduced when compared with the agar and karaya gum. Viscosity of karaya gum is directly proportional to its volatile acetyl content. On heating it is assumed due to removal of volatile acetyl content, reduced the viscosity of gum. Due to swelling nature of carrier (Agar), the extensive surface of the carrier is increased during disintegration and dissolution rate of deposited drug is reduced. So on modification, the swelling nature and viscosity of modified natural gums was less and hence could enhance dissolution rate [13, 14].

Solid dispersions of agar, treated agar, karaya gum, modified karaya gum, PEG4000 and PEG 6000 as carrier in the ratios of 1:2, 1:4, 1:6, 1:8, 1:10 were prepared by physical mixture method and kneading method. They were evaluated for assay, solubility, practical percentage yield, pre-compression parameters and dissolution studies.

The assay values for the formulations F1 to F30 ranged from 93.7±0.14 % to 97.62±0.14 % and for the formulations K1 to K30 ranged from 90.28±0.16 % to 97.35±0.15 %. The solid dispersions complied with the requirements of assay. The solubility study was carried out in water. The solubility values for the formulations F1 to F30 ranged from 0.185±0.08 mg/ml to 0.552±0.12 mg/ml and for the formulations K1 to K30 ranged from 0.431±0.11 mg/ml to 0.561±0.14 mg/ml. There is a significant increase in the solubility of solid dispersions in distilled water as compared to fenofibrate (0.018±0.12 mg/ml). The practical percentage yield values for the formulations F1 to F30 ranged from 96.33±0.15% to 96.95±0.11% and for the formulations K1 to K30 ranged from 95.16±0.15 % to 95.29±0.11%. The results for assay, solubility and percentage yield of physical mixture solid dispersions are given in Table 4 and results of kneading method solid dispersions are given in Table 5. The assay values indicated that the drug content is uniform in the batch of solid dispersion. The improvement in solubility may be due to changing in the crystal forms, different habit, structure, surface modification. In comparison of solid dispersions by natural carriers and synthetic carriers, K30 formulation (PEG 6000 as carrier) showed maximum solubility of 0.561±0.14mg/ml.

Table 4: Characterization of physical mixture solid dispersions

Formulation Code	Assay %	Solubility (mg/ml)	% Yield
F1	93.7±0.14	0.185±0.08	96.33±0.15
F2	95.42±0.10	0.208±0.01	98.2±0.14
F3	97.71±0.14	0.224±0.09	97.67±0.25
F4	99.42±0.24	0.240±0.07	98.33±0.02
F5	98.82±0.15	0.282±0.14	98.34±0.15
F6	94.51±0.24	0.192±0.11	98.25±0.15
F7	95.42±0.15	0.211±0.09	97.29±0.14
F8	98.84±0.11	0.229±0.07	95.41±0.25
F9	97.63±0.15	0.243±0.14	98.34±0.02
F10	96.69±0.15	0.287±0.21	96.52±0.15
F11	90.28±0.14	0.210±0.11	96.41±0.14
F12	92.3±0.14	0.264±0.09	99.00±0.16
F13	93.71±0.23	0.320±0.07	98.82±0.14
F14	96.57±0.24	0.374±0.08	98.05±0.23
F15	98.82±0.14	0.480±0.12	97.95±0.11
F16	90.85±0.14	0.217±0.01	94.08±0.15
F17	93.71±0.10	0.286±0.19	98.35±0.14
F18	98.28±0.04	0.332±0.11	98.67±0.25
F19	96.00±0.24	0.369±0.14	98.38±0.02
F20	99.42±0.15	0.490±0.10	98.27±0.15
F21	94.31±0.18	0.408±0.15	95.07±0.18
F22	92.87±0.12	0.426±0.09	96.45±0.15
F23	95.38±0.14	0.464±0.17	98.45±0.23
F24	97.25±0.26	0.507±0.12	96.51±0.08
F25	96.11±0.16	0.543±0.16	97.27±0.14
F26	92.67±0.18	0.431±0.11	95.31±0.14
F27	93.24±0.18	0.453±0.09	98.12±0.16
F28	95.44±0.23	0.476±0.07	97.82±0.14
F29	98.21±0.24	0.516±0.08	98.05±0.23
F30	97.62±0.14	0.552±0.12	96.95±0.11

Values are expressed as mean±SD, n=3

Table 5: Characterization of kneading method solid dispersions

Formulation Code	Assay %	Solubility (mg/ml)	% Yield
K1	90.28±0.16	0.431±0.11	95.16±0.15
K2	88.00±0.11	0.453±0.09	97.9±0.14
K3	98.88±0.14	0.476±0.07	97.82±0.25
K4	95.42±0.23	0.516±0.08	98.52±0.02
K5	96.57±0.17	0.552±0.12	98.38±0.15
K6	93.62±0.24	0.198±0.11	93.21±0.18
K7	94.51±0.16	0.216±0.09	96.25±0.12
K8	97.64±0.12	0.235±0.06	94.51±0.27
K9	98.81±0.15	0.251±0.16	97.35±0.04
K10	96.74±0.15	0.293±0.22	98.34±0.11
K11	89.14±0.14	0.206±0.11	94.91±0.14
K12	92.57±0.14	0.267±0.09	98.35±0.18
K13	94.84±0.29	0.325±0.07	98.35±0.17
K14	90.85±0.22	0.382±0.08	98.41±0.26
K15	96.57±0.14	0.487±0.12	98.00±0.14
K16	91.23±0.14	0.213±0.01	94.12±0.15
K17	93.65±0.10	0.277±0.13	98.26±0.14
K18	97.28±0.14	0.318±0.17	98.36±0.25
K19	95.42±0.24	0.382±0.08	98.67±0.02
K20	96.53±0.15	0.497±0.14	97.29±0.15
K21	90.28±0.16	0.413±0.09	94.16±0.15
K22	92.21±0.11	0.430±0.13	97.9±0.14
K23	97.88±0.14	0.468±0.09	95.82±0.25
K24	95.42±0.23	0.512±0.07	96.52±0.02
K25	94.57±0.17	0.549±0.13	98.38±0.15
K26	91.26±0.24	0.435±0.11	94.21±0.18
K27	97.15±0.16	0.458±0.09	96.52±0.12
K28	96.45±0.12	0.481±0.06	94.15±0.27
K29	98.21±0.15	0.522±0.16	96.35±0.04
K30	97.35±0.15	0.561±0.14	95.29±0.15

Values are expressed as mean±SD, n=3

The Solid dispersions prepared by physical mixture method and kneading method were evaluated for pre compression parameters. Angle of repose for the formulations F1 to F30 and K1 to K30 ranged from 25.46±0.16ºθ to 32.12±0.25ºθ and 20.32±0.22ºθ to 31.39±0.29ºθ respectively. Carr's index from bulk density and tapped density ranged from 2.59±0.31% to 6.22±0.71% for F1 to F30 physical mixture solid dispersions and 3.03±0.01% to 8.20±0.57% for K1 to K30 kneading method solid dispersions respectively. Hausner's ratio ranged from 1.02±0.21 to 1.11±0.41for F1 to F30 and 1.02±0.09 to 1.15±0.42 for K1 to K30 respectively. All the formulations exhibited excellent flow property.

In vitro dissolution studies of all the formulations were performed and it was observed as the ratio of carrier increased the dissolution rate was faster. As solubility is directly proportional to dissolution based on solubility optimization of formulation is done. Enhanced solubility is seen in formulations F5, F10, F15, F20, F25, F30 and K5, K10, K15, K20, K25, K30 containing 1:10 ratio of each carrier both by physical mixture and kneading method solid dispersions. Hence dissolutions studies of these formulations were compared. Dissolution profiles for physical mixture formulations and kneading method formulations is given in Figure 2 & 3.

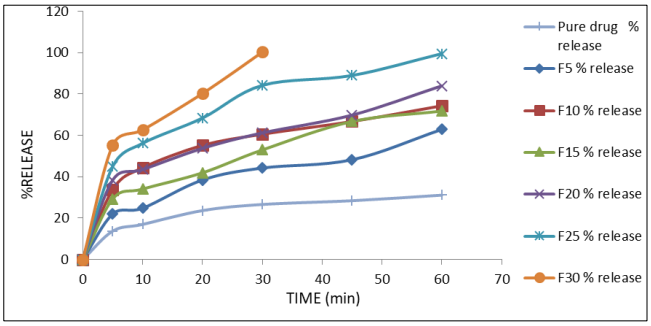

Fig 2: Percentage release profiles of fenofibrate solid dispersions by physical mixture

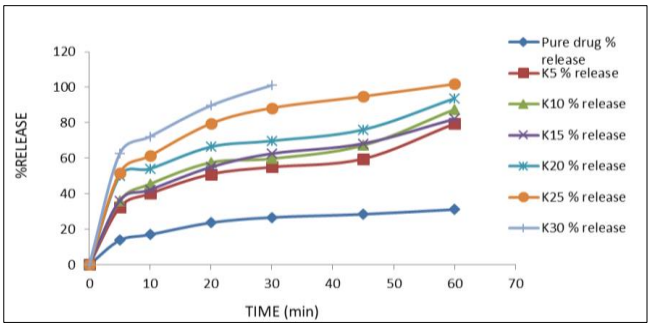

Fig 3: Percentage release profiles of fenofibrate solid dispersions by kneading method

It was observed that percentage drug release from physical mixture method of fenofibrate solid dispersions with treated agar (74.31±1.41%) and modified karaya gum (83.96±1.42%) showed faster drug release than agar (62.87±1.35%) and karaya gum (71.74±1.37%). Similarly kneading method also showed faster drug release with treated agar (87.56±1.40%) and modified karaya gum (93.73±1.35%) than agar (79.46±1.37%) and karaya gum (82.16±1.37 %). Modified gums enhanced dissolution when compared to natural gums, due to less swelling index and viscosity. Among synthetic carriers, PEG 6000 showed faster release (F30, 100.29±1.31% and K30, 101.19±1.12% in 30 minutes) than PEG 4000 (F25, 99.51±1.29% and K25, 101.83±1.14% in 60 minutes). When compared with natural carriers and synthetic carriers, PEG 6000 (synthetic carrier) showed faster drug release than natural carrier (Modified karaya gum, F20, 83.96±1.42% and K20, 93.73±1.35% in 60 minutes) in physical mixture and kneading method. The comparison graphs against pure drug is given in Figure 4.

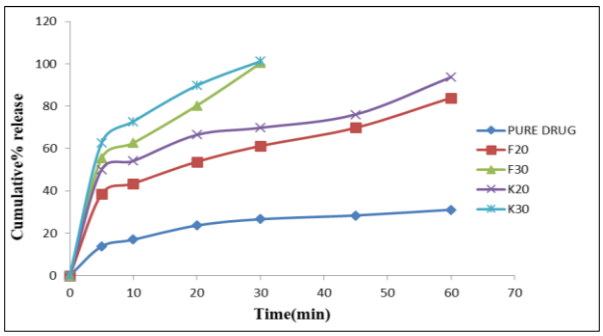

Fig 4: Dissolution profile of natural and synthetic carrier optimized with pure drug

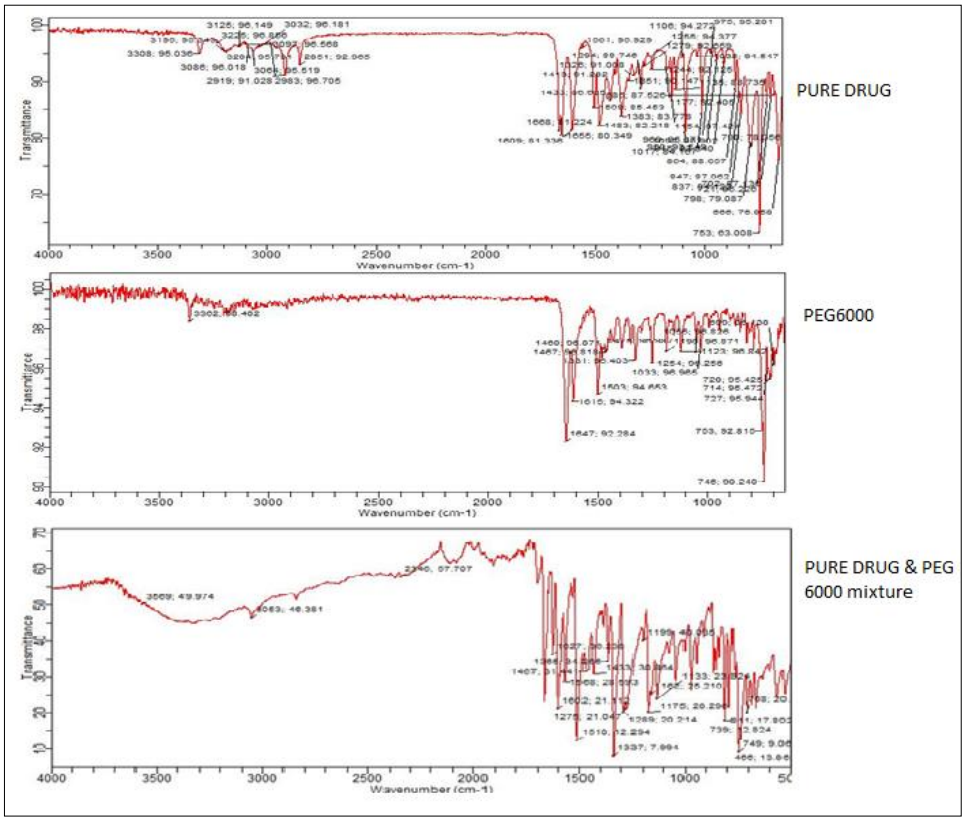

Fig 5: FTIR graphs of pure drug, PEG 6000, pure drug & PEG 6000 mixture

FTIR studies were done to verify if there was any interaction between the pure drug and various excipients employed. The various FTIR graphs both of pure drug and PEG 6000 were mixed and the blend was formulated into IR pellet and scanned using FTIR. In IR spectra the peaks representing the pure drug (3064.84, NH stretching; 3159.18, CH stretching; 1615, C=O stretching; 1595.02, CN stretching; 1483, C=C stretching) were similar in formulation spectra (pure drug & PEG 6000 mixture) indicating there was no interaction of the pure drug with excipients used in formulation. The spectra is shown in figure 5.

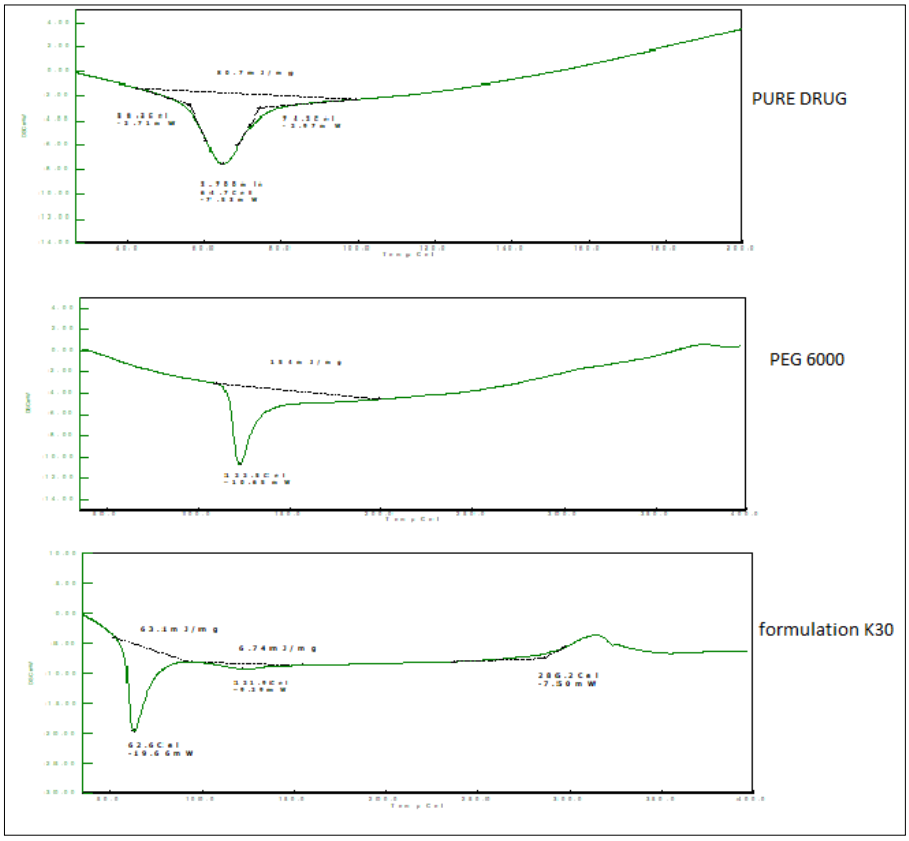

Fig 6: DSC of pure drug, PEG 6000 and formulation K30.

DSC studies of pure drug, PEG 6000 and formulation K30 were performed (given in Figure 6). The thermograms of the solid dispersions were superimposed with the plain drug to compare the results. DSC of the pure drug showed a sharp endothermic peak at 64.7ºC. The thermogram of formulation K30 was about 62.6ºC, this slight change in peak could be due to solubilisation of drug in carrier during formulation [17].

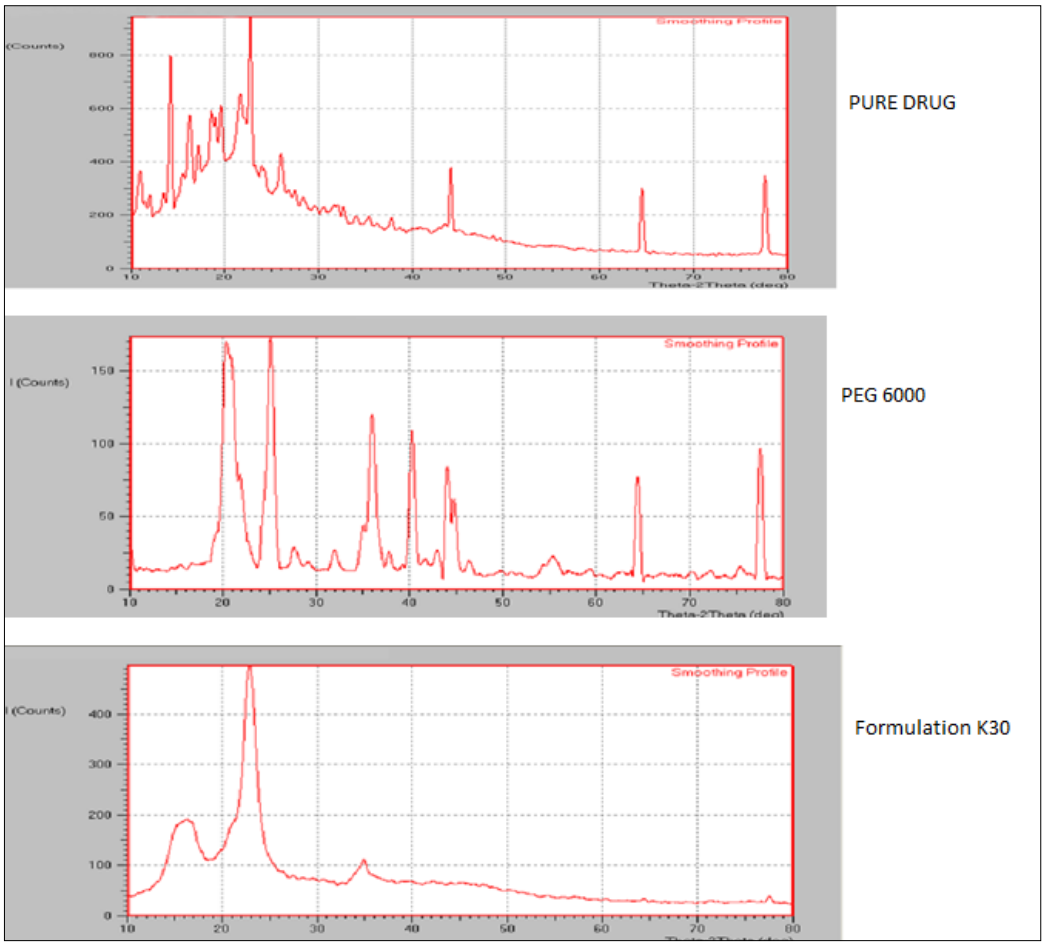

Fig 7: XRD graph of pure drug, PEG 6000 and formulation K30

The crystallinity of the prepared solid dispersions of fenofibrate is studied by XRD. The change in degree of crystallinity was studied. The pure drug and solid dispersions were also analysed by XRD in same manner and the peak intensity and presence of new peaks were noted. The XRD results are shown in figure 7 indicated that the characteristic bands obtained for the pure drug are not retained in the formulation mixture. These studies indicated that crystallinity of drug was changed with excipients used in the formulation [16].

The stability studies were performed according to ICH guidelines (40ºC±2ºC, 75%±5% RH) for 3 months for the optimised formulation K30. No change in physical appearance was observed in sampling intervals of every month and also at end of three months. No significant change was observed in assay values (97.04±0.11% at end of third month) when compared to initial result (97.35±0.15%). Dissolution profile of the formulation K30 at every sampling interval and at end of three months (100.99±0.22% in 30min) also was similar to initial (101.19±1.12% in 30 min). The stability study results indicate no significant change in evaluation parameters, hence the formulation K30 is stable.

Conclusion

To enhance solubility of fenofibrate, solid dispersions with natural carriers and synthetic carriers were prepared by physical mixture and kneading method. PEG 6000 increased solubility, and dissolution rate of the drug fenofibrate by kneading method compared with that of the pure drug. When compared to agar and karaya gum, modified forms are better than the natural forms. When compared to natural and synthetic carriers, synthetic carriers are better than natural carriers. Solid dispersion technique was successful in improving the dissolution rate of fenofibrate. The synthetic carriers like PEG 6000 were successful in improving the dissolution rate of fenofibrate by kneading method slightly when compared with physical mixture method.

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