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Formulation Development and I*n Vitro* Evaluation of Immediate Release Fenofibrate Pellets

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ABSTRACT

The present study was aimed to formulate and evaluate immediate release fenofibrate pellets using pan coater. Fenofibrate, anti lipidemic drug, being water insoluble with a half life of 22.1 h suitable to develop immediate release pellets for the treatment of primary hypercholesterolemia. Eight formulations (F1-F8) of fenofibrate pellets were prepared using a combination of $PVPK_{30}$ as binder and starch as a disintegrant. The prepared pellets were subjected to micrometric properties and *In vitro* drug release studies. The optimized formulation, F8, showed 99.1% drug release in 30 min. Scanning electron microscopy (SEM) studies showed that the prepared pellets are spherical in shape. The release profile for optimized formulation (F8) was comparable and found higher release than the marketed formulation (LIPICARD) for fenofibrate. The mathematical model was built on the hypotheses that drug diffusion and drug dissolution in the release environment are the key phenomena affecting drug release kinetics and drug release was found to be followed first order with dissolution mechanism.

Keywords: Fenofibrate; pelletization; immediate release; $PVPK_{30}$.

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INTRODUCTION

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semispherical solid units typically from about 0.5 - 1.5 mm[1,2]. These are intended usually for oral administration. Pellets, give more stability from compression and other stress conditions during formulation and storage conditions. Moreover, pellets being multi-unit particulate dosage forms, can offer some additional advantages such as easy dispersion in GI tract, increased drug absorption, and minimum potential for local irritation of the drug[3]. The micropellets can be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular, because of no problems of tampering[4]. The present study focused on the development of immediate release capsules containing fenofibrate pellets.

Fenofibrate is an anti-lipidemic drug, chemically it is 1-methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate, widely used as an adjunctive therapy to diet to reduce elevated LDL-C, triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb)[5]. Conventional immediate release drug delivery systems are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life.

MATERIAL AND METHODS

Bulk drug (fenofibrate) and all other excipients (sucrose spheres, $PVPK_{30}$, maize starch, sodium lauryl sulfate) were obtained as gift samples from Nosch labs Pvt ltd, Hyderabad.

Drug-Excipients Compatibility Study:

FT-IR studies: In this study, potassium bromide disc method was employed. IR studies of pure drug and physical mixtures of drugs and excipients were done. The powdered sample was intimately mixed with dry powdered potassium bromide[6,7]. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer (Schimadzu FT IR – 8700) using sample holder and spectrum was recorded.

Stability studies: The drug and excipient compatibility study was done at accelerated conditions for short period of time (40 ± 2 ˚C / 75 ± 5 % RH) and long-term conditions (25 ± 2 ˚C /60 ± 5% RH) with periodic observation and physical evaluation[8]. Samples of fenofibrate and individual excipients were intimately mixed in equal parts (1:1) ratio by weight and filled in glass vials. Samples were physically observed at the end of 1st week, 2nd week and 4th week.

Formulation development of fenofibrate Pellets:

The fenofibrate pellets were prepared by pan coating technique. Sucrose spheres (#24/#30) were taken into coating pan maintained at a speed of 15 rpm and coated with drug and binder solution along with maize starch at a spray rate of 0.8 ml/min. Continued the process of coating sucrose spheres with binding solution till sucrose spheres have to attain the required size. Unload the drug loaded pellets into clean stainless steel trays, spread them uniformly and load the trays into clean hot air dryer. The pellets were dried at 45º C for 8 h in a stainless steel tray drier, record the dryer temperature once in every 30 min. After completion of drying process, moisture content was checked and found to ensure it is not more than 2.5%. The dried pellets were passed through sifter to remove the lumps. Drying process was continued till minimum weight was gained.

Formulation trials: Formulation studies of fenofibrate immediate release pellets are based on preformulation data of various excipients selected and their compilation as shown in the Table 1.

Ingredients (mg)	#Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Fenofibrate	200	200	200	200	200	200	200	200
Maize starch	-	-	40	20	30	40	20	50
PVP-K_{30}	-	30	-	20	30	30	10	10
Sucrose spheres (24 # 30)	110	80	70	70	50	40	80	50
Ethanol (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 1: Formulae used for the preparation of fenofibrate pellets.
#Weight of each unit = 310 mg.
Number of units in a batch = 50 capsules.

Evaluation of pellets:

The following tests are conducted to evaluate the formulated pellets of fenofibrate.

Moisture content: It is determined with Karl-Fischer (KF) method. About 30 to 40 ml of methanol is taken into titration vessel and the solvent is neutralized with standard K.F. reagent, then 0.3 g of the powdered pellet sample was accurately weighed and transferred into titration vessel. The contents are titrated with Karl Fischer reagent to end point and determined the moisture content.

Infrared spectroscopy analysis of drug and excipients: FT-IR spectra were obtained using FT-IR spectrometer (Model Schimadzu 8700) by the conventional KBr pellet method. The samples were grounded gently with anhydrous KBr and compressed to form pellet and recorded the spectrum.

Flow properties: Bulk and tapped density of pellets was determined using USP bulk density apparatus. The bulk

density, tapped densities were determined initially from which Hausners ratio was calculated. The angle of repose was determined using fixed funnel method.

Sieve analysis: A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) (sieve # 10, 14, 20 and 25). Twenty grams of fenofibrate pellets was weighed accurately and transferred to sieve # 10 which was kept on top. The sieves were shaken for 10 min. Then the pellets retained on each sieve were taken, weighed separately and amount retained was expressed in terms of percentage.

Abrasion resistance: A pre-weighed sample (approximately 10 g) was placed in an abrasion drum that was configured to raise and drop the pellets from 200 mm. The stress levels on pellets were enhanced by adding 1 mm glass beads. After 100 revolutions at 25 rpm, the mass retained on the sieve (1190 µm) was weighed and the abrasion resistance was calculated as the percentage loss of mass between initial and final weights of each pellet batch. Each batch was analyzed in triplicate.

Uniformity of weight (weight variation test): Ten capsules were randomly selected from each batch and individually weighed[9]. The average weight and standard deviation of ten capsules were calculated. The batch passes the test for weight variation if the % deviation is within the permissible limits (± 5%).

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Pellet shape analysis: To understand changes in the surface morphology, the topography of pellets was analyzed with the help of scanning electron microscopy. A small amount of pellets was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 4 kV, chamber pressure of 19.7 mm Hg at different magnification levels.

Estimation of drug content for fenofibrate:

Equivalent to 250 mg of drug accurately weighed, which is initially dissolved with few drops of ethanol and made up to the mark in 250 ml volumetric flask. Now the mixture is filtered and from this 1 ml of filtrate taken separately in a 100 ml volumetric flask which is diluted up to the mark with ethanol. The drug content was estimated by UV spectrophotometer at λmax of 286 nm against blank. The content uniformity should be not less than 95 % and not more than 105 % of the labeled value.

***In vitro* release studies for fenofibrate pellets:**

In vitro drug release was determined using a USP Type-II dissolution testing apparatus (paddle method). Weigh accurately about 310 mg of fenofibrate pellets filled into each capsule and placed in each of the dissolution flasks, containing 1000 ml of dissolution medium (0.1 M SLS), previously which has been equilibrated to the temperature of 37 ± 5 ºC. Immediately start the apparatus and withdraw 5 ml samples for every 5 min up to 30 min from each vessel and replaced fresh 0.1 M SLS media and the samples are filtered. 1 ml of the filtrate is diluted to 10 ml with ethanol. The amount of fenofibrate pellets dissolved from each sample was estimated by UV spectrophotometer at λmax of 286 nm against blank and reported. Dissolution tests were performed in triplicate.

Parameter	Value
Inlet air temperature (°C)	40-45
Spray rate (ml/min)	0.8
Spray nozzle diameter (mm)	0.029
Spray pressure (Kg/Cm ^{2})	4
Pan rotation speed (rpm)	15
Pan angle (°)	45

Table 2: Parameters used during coating of fenofibrate pellets.

RESULTS AND DISCUSSION

Immediate release pellets were developed for an anti lipidemic drug with a view to deliver the drug immediately using balling/spherical agglomeration/pelletization technique. The details of results and discussion were given in the following sections.

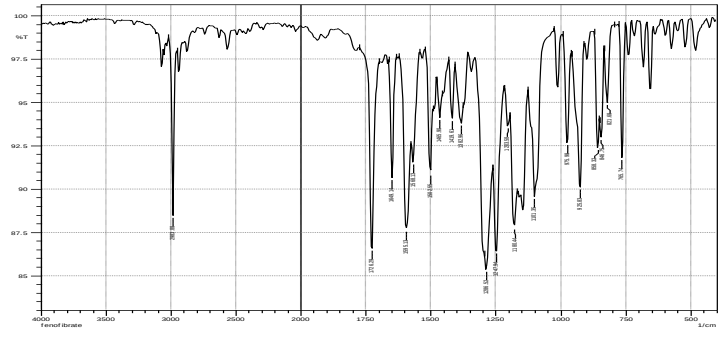
Estimation of fenofibrate:

The drug estimation was made in ethanol at λ_{max} of 286 nm using UV spectrophotometer. Calibration curve obeyed Beer – Lambert's law in the concentration range of 3-18 µg/ml (R^2 = 0.9987).

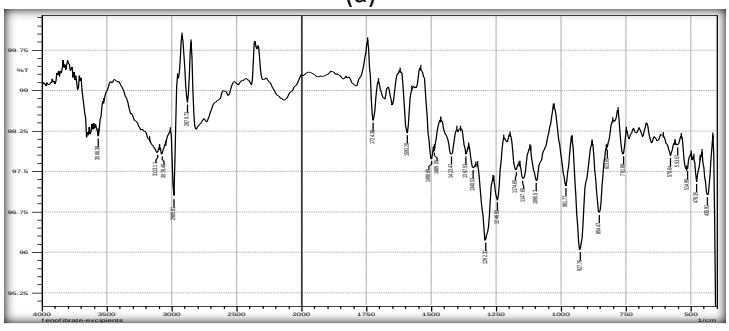
Drug-excipient compatibility studies for fenofibrate

FT-IR studies for fenofibrate:

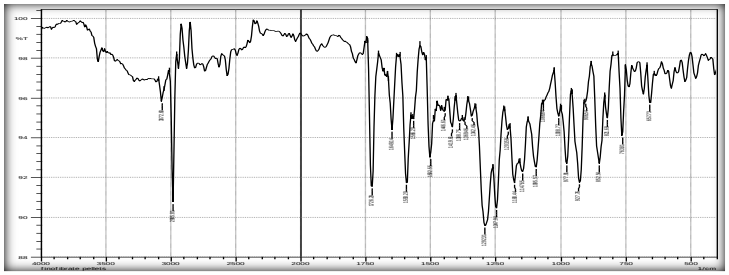
The FT-IR scans for the fenofibrate drug and for mixtures of fenofibrate with different excipients, and fenofibrate pellets are taken and reproduced in Figure 1 (a), (b) & (c).



(a)



(b)



(c)

Figure 1: FT-IR spectra of **(a)** pure fenofibrate **(b)** FT-IR spectra of fenofibrate – excipients formulation mixture. **(c)** FT-IR spectra of fenofibrate pellets.

The data obtained from the FT-IR spectrum are reported in the Table 3. The results shown in Table 3 indicated that the characteristic bands obtained for the pure drug are retained in the formulation mixture as well as in the prepared pellets. These studies indicated a *prima-facie* evidence of compatibility of drug with excipients used in the formulation.

Functional group	Bands in pure fenofibrate (cm^{-1})	Bands in formulation mixture (cm^{-1})	Bands in fenofibrate pellets (cm^{-1})
C=C stretching	1573.20	1583.20	1563.20
Chlorobenzene	925.70	823.60	821.68
Carbonyl group	1651	1724.36	1640.14
C-H stretching	2876.6	2879.72	2965.81
-OH streching	3433.2	3544.27	3072.60
-C-O-C streching	2985	2883.58	2965.81

Table 3: Characteristic bands for fenofibrate, formulation mixture and pellets obtained in FT-IR spectrum.

Characterization of fenofibrate pellets:

The formulated pellets were subjected to various tests as mentioned in materials and methods for their characterization. The data obtained from these studies are compiled and recorded in the Table 4.

A perusal to the Table 4, the results were well within the specified limits for bulk density and tapped density which further indicated that the flow properties for all the fenofibrate pellets (F1 – F8) were found to be good.

Formulation code	Parameter*		
	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner ratio
F1	0.802 ± 0.01	0.815 ± 0.001	1.02 ± 0.04
F2	0.797 ± 0.001	0.803 ± 0.002	1.00 ± 0.05
F3	0.765 ± 0.007	0.797 ± 0.002	1.04 ± 0.01
F4	0.782 ± 0.007	0.810 ± 0.001	1.03 ± 0.01
F5	0.755 ± 0.002	0.799 ± 0.002	1.06 ± 0.02
F6	0.710 ± 0.001	0.736 ± 0.001	1.03 ± 0.05
F7	0.723 ± 0.002	0.797 ± 0.001	1.10 ± 0.04
F8	0.756 ± 0.001	0.805 ± 0.007	1.06 ± 0.05

Table 4: Flow properties for fenofibrate pellets.

*****Each value is an average of three trials ± S.D.

Particle size distribution: The various formulations of fenofibrate pellets (F1 to F8) are subjected for particle size distribution by sieve analysis. The percentage of pellets retained on different sieves after shaking the sieve shaker for the specified period for all eight formulations are obtained. From the obtained results, the particle size distribution data reveals that, all the formulations passed the tests for size distribution analysis.

Physicochemical characterization for fenofibrate pellets:

The prepared pellets (F1 to F8) were subjected to physicochemical characterization. The results obtained from these studies are recorded in the Table 5.

A perusal to Table 5, weight variation of pellets ranges from 234 to 281 mg and observed within the specifications. Abrasion resistance (%) was found to be less than 1 for all formulations. The % moisture content ranges from 1.22 to 1.57 for the different formulations (F1 to F8). Assay results were found to be well within the limits for all 8 formulations (95 to 98.5%).

Formulation code	Parameter*			
	Uniformity of weight (mg)	Abrasion resistance (%)	Moisture content (%)	Assay (%)
F1	279.3 ± 0.625	0.55 ± 0.07	1.38 ± 0.41	95.1 ± 0.01
F2	277.9 ± 0.685	0.805 ± 0.14	1.22 ± 0.05	95.2 ± 0.06
F3	234.1 ± 0.692	0.82 ± 0.014	1.32 ± 0.12	96.3±0.007
F4	281.2 ± 0.539	0.58 ± 0.06	1.51 ± 0.02	97.2 ± 0.42
F5	280.4 ± 0.908	0.710 ± 0.14	1.46 ± 0.04	97.2 ± 0.28
F6	280.7 ± 0.658	0.57 ± 0.028	1.57 ± 0.09	96.8 ± 0.09
F7	279.6 ± 0.859	0.635 ± 0.02	1.56 ± 0.20	95.6±0.042
F8	277.3 ± 0.760	0.71 ± 0.04	1.27 ± 0.31	98.5 ± 0.05

Table 5: Physicochemical characterization for fenofibrate pellets

Dissolution profile for fenofibrate pellets:

The *in vitro* drug release studies were carried out as per procedure mentioned in the materials and methods. The data obtained from the dissolution studies for the formulations F1 to F8 are given in the Table 6 and is recorded in the Fig 2. A perusal to the Figure 2 and Table 6, it is evident that the drug release was found to be in the range of 14.63 - 99.10% for the formulations F1 to F8 in 30 min. This indicated that the drug release was not consistent for all the formulations. The effect of PVP-K_{30} and maize starch concentration on the drug release was clearly indicated in the release studies. The release was not complete for the formulations F1 to F4, indicated the presence of maize starch (disintegrant) for the dug release. Further, the optimum levels of starch, $PVPK_{30}$ and sucrose spheres are also essential to release the drug completely

and consistently as is evidenced by the formulation, F8. Hence, the formulation F8 was used to compare with the marketed formulation (LIPICARD).

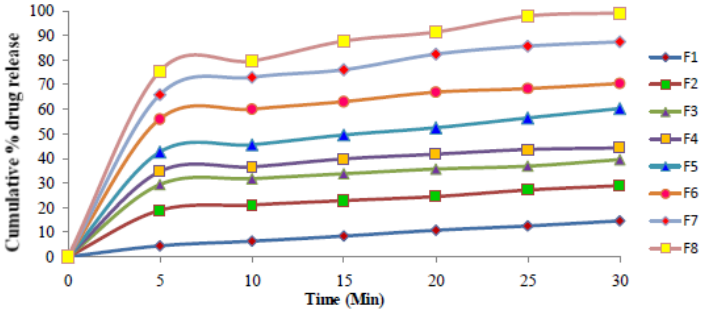


Figure 2: *In vitro* dissolution profile obtained for the fenofibrate pellets from formulations F1 to F8.

The comparative dissolution profile for F8 and Lipicard is shown in the Figure 3 indicated that the release for F8 is comparable and even greater than the marketed formulation.

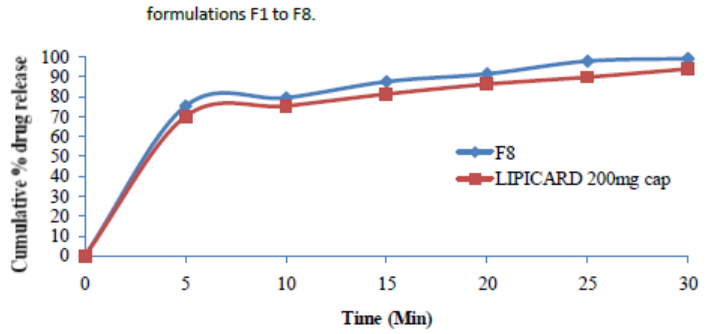


Figure 3: *In vitro* dissolution profile for the optimized fenofibrate formulation F8 and marketed capsule 'Lipicard'.

Pellet shape analysis by scanning electron microscopy for fenofibrate pellets:

Acceptable shape was obtained indicating perfect sphericity of pellets as shown in Figure 4 (a), (b) and (c).

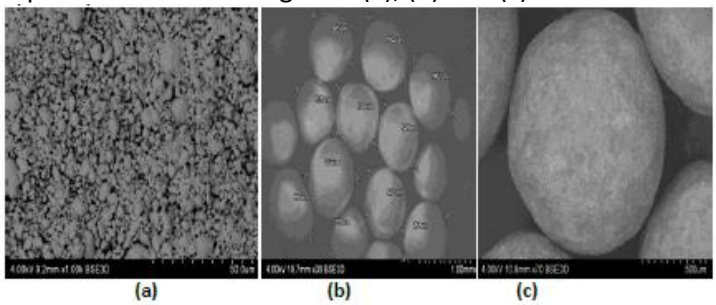


Figure 4: SEM photographs of fenofibrate pellets F8 (a) 1 x magnification (b) 30 x magnification. (c) 70 x magnifications.

Kinetics of drug release from optimized formulation of fenofibrate:

The release studies obtained for optimized formulation F8 was subjected for kinetics of drug release. The regression coefficient values are higher for F8 with first order and therefore the release kinetics followed first order. Hixson – Crowell cube root law and Higuchi's models were applied to test the release mechanism. The R^2 values are higher for Hixson – Crowell cube root law in comparison to Higuchi model and hence, release mechanism followed dissolution rate controlled process.

Time (Min)	% Cumulative drug release* (A.M. ± S.D.)								
	F1	F2	F3	F4	F5	F6	F7	F8	Marketed capsule (Lipicard)
0	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00 ± 0.000	0.00± 0.000	0.00 ± 0.000	0.00 ± 0.000
5	4.50± 0.40	9.44± 0.438	29.3 ± 0.0780	34.6± 0.171	42.54± 0.272	55.95± 0.091	65.92±0.153	75.41± 0.450	70.05± 0.344
10	6.30± 0.20	11.45±0.548	31.76± 0.120	36.5± 0.107	45.53± 0.191	60.03± 0.22	72.99± 1.267	79.56± 0.330	75.3 ± 0.15
15	8.43± 0.404	13.85±0.076	33.73± 0.207	39.7± 0.125	49.51± 0.645	63.03± 0.157	76.03± 0.198	87.67± 0.106	81.29 ± 0.14
20	10.83± 0.513	15.49±0.453	35.66± 0.095	41.7± 0.239	52.42± 0.18	66.94± 0.919	82.4 ± 0.358	91.41± 0.166	86.25 ± 0.07
25	12.50± 0.05	17.29±0.125	36.85± 0.087	43.6± 0.153	56.4 ± 0.577	68.37± 0.165	85.66± 0.104	97.89± 0.087	89.81 ± 0.035
30	14.63± 0.379	19.44±0.242	39.53± 0.120	44.2± 0.136	60.28± 0.845	70.47± 0.865	87.41± 0.164	**99.10± 0.186**	**93.91± 0.020**

Table 6: *In vitro* dissolution data obtained for the fenofibrate pellets formulations from F1 to F8.

*Each value is an average of three trials.

CONCLUSION

Oral multiparticulate drug delivery systems of immediate release fenofibrate in the form of pellets were successfully developed. The developed formulations were found to have positive impact on *in vitro* dissolution behavior. The optimized formulations showed gradual release and the release is comparable and higher than the marketed formulation. Thus, the spherical agglomeration/pelletization/balling technique using conventional pan coater has improved the drug release for fenofibrate pellets.

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