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Conseption and evaluation of Gemfibrozil as immediate drug delivery system

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Abstract

Immediate release tablets are widely used for its better therapeutic availability, in this present work a pharmaceutically equivalent, low cost quality improved formulation of Gemfibrozil as Immediate release tablets were developed Gemfibrozil is a 5-(2,5 – dimethyl phenoxy) – 2,2-dimethyl pentanoic acid which is a fibric acid derivative used in the treatment of Hyperlipidaemic by using micro crystalline cellulose, pregelatinized starch, sodium starch glycollate and calcium stearate as excipient. According to Biopharmaceutical Classification System Gemfibrozil is classified under class-II drugs(low solubility-high permeability) and it was compared with the innovator and effect of LOD on Gemfibrozil immediate release tablets were studied and to evaluated the formulations for the physical parameters such as uniformity of weight, disintegration time, friability, moisture content, thickness, hardness and drug content and the best formulations were coated with opadry white and comparative invitro dissolution profile of the coated formulation with that of the innovator product had shown that F6 formulation best matched with innovator and the formulations are loaded for the stability studies.

Key words: Gemfibrozil, Immediate release gemfibrozil, surfactant improved drug release, Effect of surfactant, BCS class-II drugs.

Introduction

Immediate Release tablets are widely used dosage forms which are designed to disintegrates and release their medicaments with no special rate controlling features such as special coatings and other techniques, immediate release tablets has advantages to releases the drug immediately, Dissolution of the drug is fast, Immediate action of the drug can be obtained, No dose dumping problems are seen[1]. Gemfibrozil which is a Biopharmaceutical classification system (BCS)

class-II drug(low solubility-high permeability) acts as lipid regulating agent which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increase high density lipoprotein (HDL) cholesterol. The reduction of LDL and increase in HDL has been shown to benefit in terms of reduced coronary heart disease. Gemfibrozil inhibits peripheral lipolysis and decreases the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil also inhibits synthesis and increases clearance of VLDL carrier apolipo protein B decreasing in VLDL production [2]. Mohammad *et al* (2008) has investigated on different levels of invitro-in vivo correlation of gemfibrozil immediate release capsule. The aim of this study was to select a dissolution conditions for gemfibrozil immediate release capsule resulting in best invitro correlation [3]. Mallikarjuna *et al* (2008) worked on Aceclofenac fast-dispersible tablets have been prepared by wet granulation method. Effects of super disintegrates such as croscarmellose sodium, sodium starch glycollate and crospovidone on wetting time, disintegration time, drug content, invitro release and stability parameters has been studied, where as disintegration time and dissolution parameters increased with the increase in the level of sodium starch glycollate[4]. The present works aims in developing formulation of Gemfibrozil as Immediate release tablets to improve solubility by using surfactants which would enhance its solubility, and improve its therapeutic efficacy when immediate plasma levels of the drug.

Materials and methods

Gemfibriozil procured as a gift samaple from I H, German Remedies, Microcrystalline cellulose (Avicel PH 101) purchased from FMC Biopolymers, Pregelatinized starch (Starch 1500) purchased from Colorcon, Sodium starch Glycollate (Primogel) purchased from FMC Biopolymers, Colloidal silicon dioxide(Aerosil) purchased from Degussa, Hydroxypropyl cellulose all other chemicals and solvents are of analytical grade.

2.1 Preformulation Studies

Initially preformulation studies were performed for the pure drugs to know the interaction with the exciepients used for formulate gemfibrozil immediate release tablets. The various pre formulation parameters like physical characteristics solubility and assay are studied the colour, odour and taste of the drug were recorded using descriptive terminology

2.2 Solubility

It is well known that in order for a drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then the portion into the absorbing membrane. Two of the most important physico-chemical properties of a drug that influence its absorptive behavior are its aqueous solubility and, if it is a weak acid or base (as are most drugs) it's $P_{ka.}$

The aqueous solubility of drug influences its dissolution rate, which is turn establish its concentration in solution and hence the driving force for diffusion. Dissolution rate is related to solubility as shown by Noyes- whitney which under sink condition.

$$dc/dt = K_d A C_s$$

The dissolution rate constant only if surface area remains constant but the important point is that the initial rate is proportional directly to aqueous solubility Cs. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

2.3 Compatibility Study

The interference by the excipients was evaluated by preparing a physical mixture of Gemfibrozil and each excipient in 1:1 ratio and analyzed the sample for Gemfibrozil content by spectrophotometric method. Further the KBr disk sample was prepared and spectra were obtained for pure drug, polymer, drug and polymer concentration using IR spectrophotometer.

Table: 1 Formulation of Gemfibrozil Immediate Release Tablets (900mg)

S No.	Ingredients	Quantity in mg					
		F1	F2	F3	F4	F5	F6
1	Gemfibrozil	600	600	600	600	600	600
2	Micro crystalline cellulose pH 101	52	52	52	52	37	37
3	Starch 1500	41	41	21	36	36	36
4	Low Hydroxy propyl cellulose LH21	30	40	---	---	---	---
5	Sodium starch glycollate	__	__	35	40	55	55
6	Aerosil	19	19	10	4	24	24
7	Klucel LF	10	10	10	10	10	10
8	Tween80	12	12	12	12	12	12
9	Water	---	---	----	q. s	q. s	q. s
10	Isopropyl Alcohol	q. s	q. s	q. s	q. s	q. s	q. s
11	Micro crystalline cellulose pH 200	91	92	100	66	66	66
12	Low hydroxyl propyl cellulose LH21	20	10	__	__	__	__
13	Sodium starch glycolate	__	__	35	35	35	35
14	Aerosil	16	16	16	16	16	16
15	Calcium stearate	9	9	9	9	9	9

2.4 Formulation of gemfibrozil immediate release tablet

Ingredients were accurately weighed and dispense separately. Sift MCC PH 101, pregelatinized starch Sodium starch Glycollate and Aerosil along with drug through #40mesh. Dry mix the drug and excipients in 2.0litres Rapid mixer. Tween80 Dissolved in isopropyl alcohol and stir well. klucel LF is added to the above solution and stirred well until it dissolves completely. Granulate the dry mix with binder solution up to get desired granules. Dry the granules in rapid dryer up to get the Loss on drying range between 0.5% to 1.5% at50^0c. Pass the dried granules through #30mesh. Finally ensure that all the dried granules passed through #30mesh. Weigh the extra granular excipients MCC PH 200, sodium starch Glycollate, Aerosil in accordance with the obtained yield of dried granules and pass through #40mesh. The extra granular excipients were mixed with dried granules. Weigh the Lubricant calcium stearate and passed through #60mesh then blend it with pre lubrication blend for 5 minutes. Unload the blend compress with 19.0*9.1mm punches debossed with “E” on upper punch and “82” on lower punch. In table no: 1 shows the different formulations and there proportion of excipients.

2.5 Coating Procedure

Opadry white is dispensed in required quantity of water and stir 30 minutes then required quantity of Isopropyl alcohol was added and stirred for 15 minutes until it dispersed completely. Gemfibrozil Immediate release tablets were coated by using Gans coater (Gansons .Ltd, Malasia) setting Inlet Temperature at 40^0c Exhaust temperature at 30^0c Piston pump RPM at 6-7, Pan RPM at 7-8 Solid Content 6% Gun to bed distance of 13-14cm.

2.6 *In-Vitro* Dissolution Study

Invitro dissolution carried out for a period of 30 minutes in the dissolution medium (900ml) 0.2M Phosphate buffer pH7.5 by using USP type II paddle and maintained 37±0.5ºc at 50 r.p.m sampling was done at specific time intervals 5,10,15,30 minutes and the samples were evaluated by using AZT using a double beam UV-Visible spectrophotometer (V- 570, Jasco, Tokyo, Japan) at 267nm for 7.5 ph buffer.

2.7 Statistical Analysis

All statistical calculations were performed using Sigma Stat 3.5 demo version software. Data were analyzed using student's' test and one way analysis of variance (ANOVA). Differences were considered statistically significant at $P<0.05$.

Table 2: Pre Formulation Studies

Physical characterization	Results
Organoleptic properties:	
Color	white color
state	Waxy crystalline solids
Taste	Taste less
Flow properties:	
Bulk Density	0.217 g/cm^3
Tapped Density	0.348 g/cm^3
Hausner's ratio	1.26
Compressibility Index	37.14%
Solubility studies:	
Water	0.06mg/ml
0.1 N HCLs	0.02 mg/ml
pH4.5Acetate buffer	0.01mg/ml
pH 6.8 phosphate buffer	0.74mg/ml
pH7.2phosphate buffer	1.45mg/ml
pH7.5 0.2M phosphate buffer	2.11mg/ml
Analytical Method	
Spectroscopy	λ max 276nm
Assay	99.8%

Results & Discussion

3.1Pre formulations studies:

Pre formulation studies were carried out which includes assay, compressibility for Bulk Density, Tapped Density, Hausner's ratio, Compressibility Index, solubility studies were carried out and the results were tabulated in table no: 2

3.2 Compatibility Study:

Compatibility studies were performed using IR spectrophotometer (Thermo.Nicolate IR-200). The IR spectrum of pure drug and physical mixture of drug and polymers were studied.

Fig: 1 IR SPECTRA OF GEMFIBROZIL

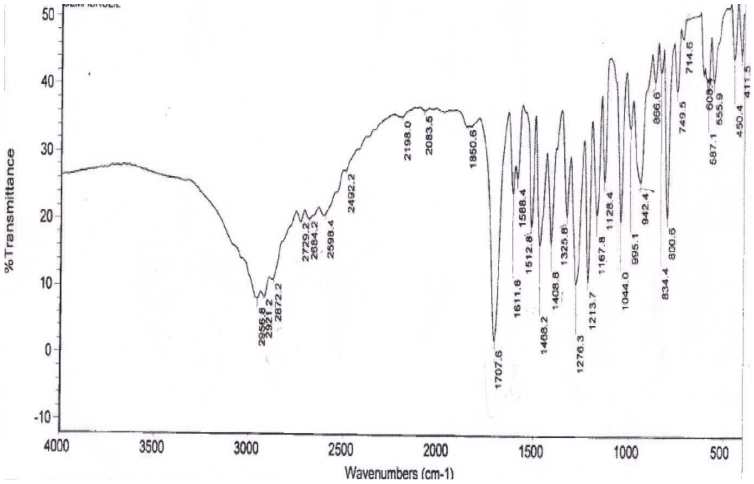
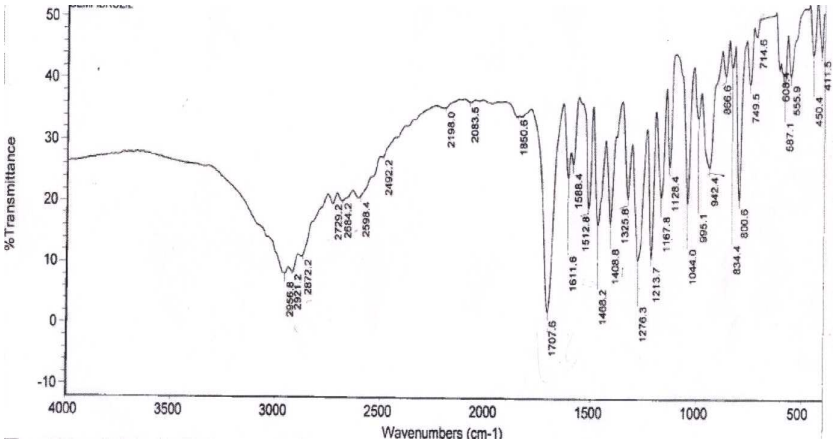


Fig: 2 IR SPECTRA OF GEMFIBROZIL + HYDROXYPROPYL CELLULOSE



The characteristic absorption peaks of Gemfibrozil were obtained at wave numbers 2956 cm-1, 1707cm-1, 1611cm-1, 1512cm-1, 1468cm-1, 1276cm-1, 1213cm-1, 1128cm-1,749cm-1.The values were summarized in figure 2-5 reveals that there is no interference between excipients and the drug. The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

Fig: 3 IR SPECTRA OF GEMFIBROZIL +SODIUM STARCH GLYCOLATE

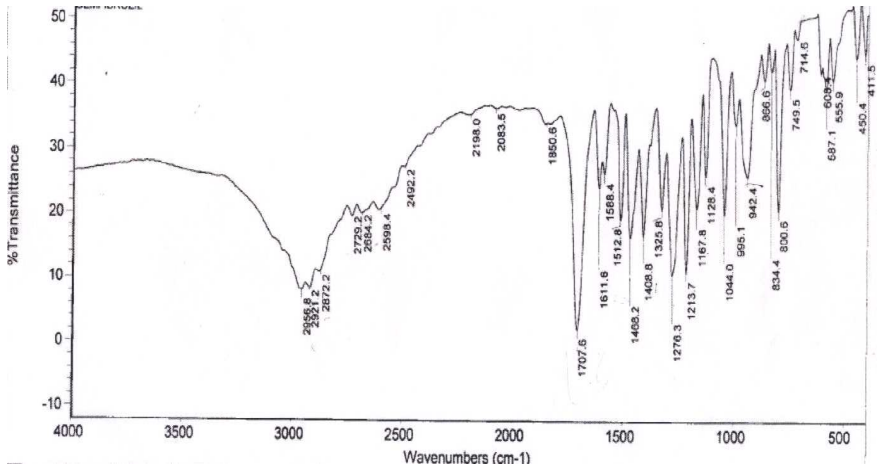
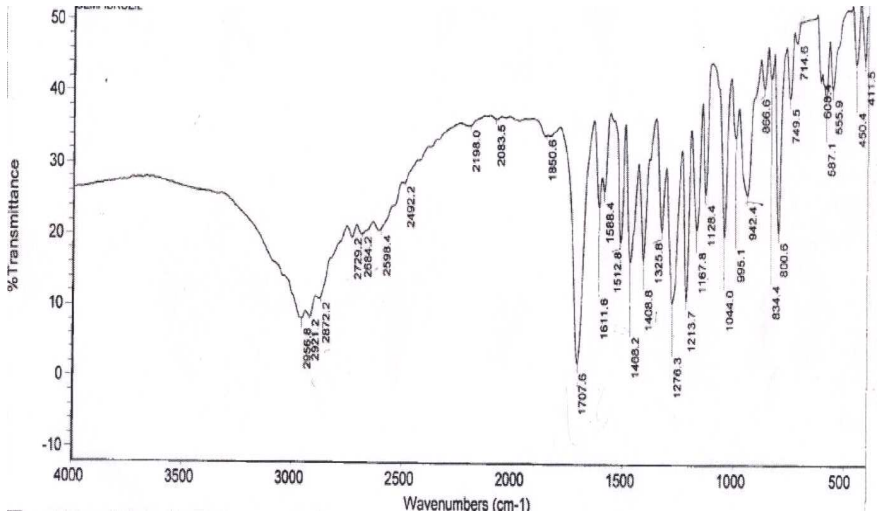


Fig: 4 IR SPECTRA OF GEMFIBROZIL+PREGELATINIZED STARCH



3.3 *In-Vitro* evaluation of tablets:

Hardness, Friability, Thickness:

Hardness of each formulation was analyzed. The formulations F1, F2, F3, F4, F5, and F6 were found to have good hardness so they were taken for further studies. The measured hardness of tablets of each batch range between11.8 to 17.8 k P, Tables mean thickness were almost uniform in all formulations and were found to be in the range of 7mm to 8mm. Friability values are found to be less than 1% in all cases and considered to be satisfactory.

Weight variation, disintegration:

The total weight of each formulation was not maintained constant however the weight variation of the tablets was within limits of 5% In case of tablets prepared with different diluents, it was observed that granulation containing LHPC21shown more disintegration time than sodium starch Glycollate, because LHPC21have more tendency to form strong bonds with other ingredients compared with other diluents

Whereas tablets prepared with different disintegrants (when used by intra granular and extra granular) it was observed that time of addition of disintegrants was a significant step because it

was found that disintegrants added at the time of intra granulation shows less disintegration time than addition of disintegrants at the time of extra granulation.

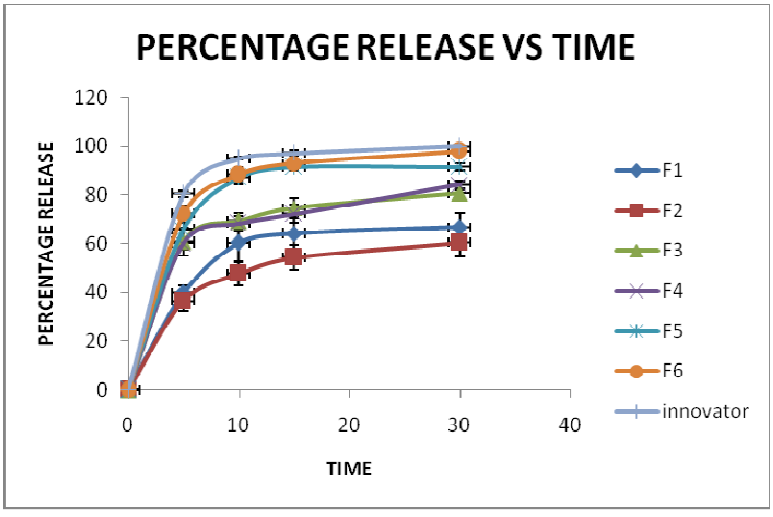
***In-vitro* dissolution study:**

In vitro dissolution study of formulations F1 to F6 were carried out in 0.2 M PH 7.5 phosphate buffer and percentage of drug release was calculated, all the formulations were kept for 30min. It was found that the above formulations meet the standard limits (80% drug release in 30min). The formulations F1, F2, F3, F4, F5, F6, were taken for coating with opadry white. The Dissolution profile of each formulation was compared with that of the innovator product. When compared to F1, F3, F5 formulation F6 having similar values of percentage drug release with that of the innovator. The results were tabulated in table no: 3 and figure no: 5 showing the percentage of drug release vs. time (minutes).

Table 3: Dissolution Study(Percentage Release Vs Time)

Time (mins)	F2	F3	F4	F6	F8	F9	Innovator
5 mins	39.86±2.7	36.43±4	60.8±5	60.27±2.3	65.9±8.1	72.2±3.6	80.53±1.4
10 mins	60.3±7.8	47.66±5	69.19±3	68.29±3.1	87.2±2.8	88.46±2.8	95.03±0.7
15 mins	64.16±7.2	54.23±5	74.59±4	72.27±3.6	91.57±1.7	93.01±1.3	97.26±1.0
30 mins	66.63±6.1	60.36±5	80.79±1	84.22±1.5	91.57±1.7	98.0±1.0	99.94±0.3

Fig: 5 Zero Order Graph



Conclusion

Gemfibrozil immediate release tablets were formulated by using microcrystalline cellulose, pregelatinized starch, sodium starch glycollate, Aerosil. Klucel LF and Tween80 were used as binders, calcium stearate was used as lubricant. Compatibility studies were carried out by using IR spectrophotometer and the drug was found to be compatible with all excipients used in different formulations. The granules were compressed in to tablets were analyzed for the

parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness, moisture content and drug content. Hardness of each formulations were analyzed. The formulation F1, F2, F3, F4, F5, F6, were found to have good hardness and were taken for further studies, Formulation containing sodium starch glycollate shows rapid rate of disintegration time, when compare with formulation containing LHPC21.The invitro dissolution profile of F6 formulation coated with opadry white was found to have equivalent percentage drug release with that of innovator product.

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