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FORMULATION AND EVALUATION OF PROLONGED RELEASE GEMFIBROZIL TABLETS

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ABSTRACT

The development of prolonged-release formulations of pharmaceuticals is essential for enhancing therapeutic efficacy and patient compliance. This study focuses on the formulation and evaluation of prolonged-release Gemfibrozil tablets, a lipid-regulating agent used in the management of hyperlipidemia. The primary objective was to design a tablet that ensures sustained release of Gemfibrozil, thereby maintaining a consistent plasma concentration over an extended period. The formulation process involved the selection of appropriate polymers and excipients to achieve the desired release profile. Various formulations were prepared using hydrophilic and hydrophobic polymers, such as hydroxypropyl methylcellulose (HPMC) and ethylcellulose, through direct compression and wet granulation techniques. The tablets were then evaluatedfor their physical characteristics, including hardness, friability, and uniformity of weight. In vitro dissolution studies were conducted using USP type II apparatus to determine the release kinetics of Gemfibrozil from the formulations. The optimized formulation demonstrated a sustained release of Gemfibrozil over 12 hours, following a non-Fickian diffusion mechanism. The release kinetics were best described by the Korsmeyer-Peppas model, indicatinga combination of diffusion and erosion mechanisms. Stability studies conducted at accelerated conditions showed that the prolonged-release tablets maintained their physical integrity and drug release profile over a period of six months.

KEYWORDS: Gemfibrozil, prolonged-release, sustained release, formulation, in vitro evaluation, polymers, drug release kinetics, stability studies.

INTRODUCTION

Hyperlipidemia, characterized by elevated levels of lipids in the blood, is a significant risk factor for cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke. Effective management of hyperlipidemia is critical to reducing cardiovascular morbidity and mortality. Gemfibrozil, a fibric acid derivative, is commonly prescribed to lower triglyceride levels and increase high-density lipoprotein (HDL) cholesterol, thus playing a crucial role in the management of hyperlipidemia.

Despite its therapeutic benefits, the conventional immediate-release formulations of Gemfibrozil require multiple daily administrations, typically two to three times a day. This frequent dosing can lead to poor patient adherence, fluctuating plasma drug levels, and suboptimal therapeutic outcomes. Prolonged-release (PR) formulations offer a solution by providing a controlled and sustained release of the drug, ensuring steady plasma concentrations over an extended period and enhancing patient compliance.

The development of prolonged-release Gemfibrozil tablets involves the strategic selection of polymers and excipients that can modulate the drug release rate. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and hydrophobic polymers like ethylcellulose (EC) are commonly used in matrix systems to achieve sustained drug release. These polymers can create a gel barrier that controls the diffusion of the drug, thus prolonging its release.

Materials: Gemfibrozil, Hydroxypropyl Methylcellulose (HPMC), Ethylcellulose (EC), Microcrystalline Cellulose (MCC), Lactose, Magnesium Stearate, Talc, Phosphate Buffer (pH 6.8), Ethanol, Water.

Method of Preparation

Preformulation Studies

Preformulation testing is an investigation of the physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. Preformulation studies yield necessary knowledge to develop a suitable formulation and provideinformation needed to define the nature of the drug substance and develop the dosage form. The following preformulation studies were performed for the obtained sample of the drug:

1. **Organoleptic Evaluation-** The color, odor, and taste of Gemfibrozil wereevaluated and described using descriptive terminology.
2. **Particle Size Distribution-** 10.35 grams of the sample was taken and added to an assembly of sieves consisting of ASTM sieve numbers #30, 40, 60, 80, 100, and 120 base plates. The assembly was closed, kept on a sieve shaker, and the analysis was started. Weights retained were checked every 5 minutes, and the process continued until variation in weights retained was not more than 5% or 0.1 grams, with 20 minutes set as the endpoint. Calculations were made to obtain cumulative percentage weight retained and tabulated.

3. **Drug-Excipient Compatibility Study**

Physical Observation: Physical mixtures of the drug and excipients were prepared by grinding specific ratios of the drug and excipients in a mortar. A sample of 3-4 grams was taken, loaded in a glass vial, covered with a rubber stopper, sealed with an aluminum cap, and labeled properly. Samples were observed, and the color was recorded for initial evaluation and loaded into a stability chamber at 40°C and 75% relative humidity for a 4-week compatibility study. Samples were removed at 1-week intervals for four weeks and observed for any color change.

4. **UV Method Development for Estimation of DrugPreparation of Different Buffer Media**

- **pH 1.2:** 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M KCl solution, and the volume was made up to 200 ml.
- **Phosphate Buffer pH 6.8:** Place 6.8 g of potassium dihydrogen phosphate and 0.896 g of sodium hydroxide in a 1000 ml volumetric flask, then add water to volume and mix.

Standard Stock: 100 mg of Gemfibrozil was added to respective media in a 100 ml volumetric flask, and the

volume was made up to 100 ml, resulting in a standard stock solution of 1 mg/ml.

Working Stock: From the above standard stock solution, 10 ml was taken and added to respective buffer media in a 100 ml volumetric flask, and the volume was made up to 100 ml to obtain 100 µg/ml solutions. Dilutions were prepared using respective media.

Determination of Absorption Maxima: A 10 µg/ml solution was taken to determine absorption maxima. Initially, a blank buffer solution was scanned in the region of 200-400 nm. Then, the sample was scanned in the same region. Absorption maxima were found to be 242 nm. Hence, all further analysis was carried out at 242 nm for pH 1.2 and pH 6.8 buffers.

Determination of Beer's Law Range and Plotting of Calibration Curve: From the working stock solution, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ml of sample was taken and diluted up to 10 ml using respective buffer media in a 10 ml volumetric flask, resulting in concentrations of 10, 20, 30, 40, 50, 60, 70, 80, 90,and 100 µg/ml solutions. These were analyzed at 242 nm, and a calibration curve was plotted, taking concentration in µg/ml on the X-axis and absorbance units on the Y-axis.

Saturation Solubility

Excess drug was carefully added using a spatula to 10 ml of the aqueous buffer in a conical flask while stirring until a heterogeneous system (solid sample and liquid) was obtained. The solution containing excess solid was then capped and stirred at 150 rpm at room temperature for 24 hours. The solution was filtered using a 0.22 µm PVDF filter, and appropriate dilutions were made and analyzedusing a UV spectrophotometer.

METHOD OF PREPARATION

Development Strategy

Based on the literature search and pre-formulation studies, the following ingredients were selected for the formulation development of prolonged-release Gemfibrozil tablets.

Selection of Formulation Method

Sustained release tablets of Gemfibrozil were formulated using the following methods:

1. Direct Compression
2. Wet Granulation

1. Direct Compression

In this process, the tablets are compressed directly from powder blends of the active ingredient and suitable excipients, which will flow uniformly into the die cavity and form a firm compact.

Brief Manufacturing Procedure for the Preparation of Tablets:

Step 1: Weigh all the ingredients separately.

Step 2: Pass Gemfibrozil and the other excipients through a 40# sieve togetherand blend for 10 minutes.

Step 3: Pass magnesium stearate through a 60# sieve, add it to the blend fromstep 2, and blend for an additional 5 minutes.

Step 4: Compress the blend from step 3 into tablets using 3.0 mm roundpunches.

Composition of Gemfibrozil Formulations for Direct Compression

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gemfibrozil	300	300	300	300	300	300	300	300	300
HPMC 50 Cps	100	150	200	100	150	200	100	150	200
Ethylcellulose	50	50	50	75	75	75	100	100	100
Lactose	40	40	40	25	25	25	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10

2. Wet Granulation

Wet granulation involves the preparation of granules by adding a granulating solution to the powder blend and then drying and compressing the granules into tablets.

Brief Manufacturing Procedure for the Preparation of Tablets

Step 1: Weigh all the ingredients separately.

Step 2: Pass Gemfibrozil and other excipients through a 40# sieve together andblend for 10 minutes.

Step 3: Prepare a granulating solution using ethanol and water.

Step 4: Gradually add the granulating solution to the powder blend whilemixing to form a damp mass.

Step 5: Pass the damp mass through a suitable sieve to form granules.

Step 6: Dry the granules in an oven at 40-50°C until a constant weight isachieved.

Step 7: Pass the dried granules through a sieve to obtain uniform granule size.

Step 8: Pass magnesium stearate through a 60# sieve, add it to the granules, andblend for 5 minutes.

Step 9: Compress the blend into tablets using 3.0 mm round punches.

EVALUATION OF TABLETS

Drug Release Kinetics

Korsmeyer-Peppas Model

To determine the mechanism of drug release, 60% drug release data were fitted into the Korsmeyer-Peppas model, which describes drug release kinetics from various pharmaceutical dosage forms exhibiting non-Fickian or anomalous release behavior.

Korsmeyer-Peppas Equation

$Mt / M\infty = Ktn$

Where:

$Mt / M\infty$ = fraction of drug released at time t

K = release rate constant

n = release exponent

The n value characterizes the release mechanism of the drug

Release Exponent(n)	Drug Transport Mechanism	Rate as a Functionof Time
0.5	Fickian diffusion	t-0.5
$0.45 < n < 0.89$	Non- Fickian diffusion	tn-1
0.89	Case 2 transport	Zero order release
> 0.89	Super Case 2 transport	tn-1

To determine the exponent n, the portion of the release curve where $Mt / M\infty<0.6$ was used. Data from in vitro drug release studies were plotted as logcumulative percentage drug release versus log time.

Comparison of Dissolution Profiles

The similarity factor (f2) was used to evaluate the release profiles of variousformulations compared with the ideal release profile.

Similarity Factor Equation

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left(\frac{R_t - T_t}{R_t}\right)^2\right]^{-0.5} \times 100\right\}$$

Where:

n = number of dissolution time points

Rt and Tt = reference and test dissolution values at time t

The similarity factor (f2) ranges between 0 and 100, where 100 indicates identical dissolution profiles between the test and reference, and values below 50 indicate dissimilar profiles.

Similarity Factor Range

Similarity Factor (f2)	Significance
<50	Test and reference profiles are dissimilar
50-100	Test and reference profiles are similar
100	Test and reference profiles are identical
>100	The equation yields negative values

Stability Studies

Stability studies were conducted to assess the capacity of the formulated Gemfibrozil tablets to maintain their identity, strength, quality, and purity throughout the established specifications over the retest or expiration dating periods.

RESULTS AND DISCUSSION

Pre formulation Studies

1. Organoleptic Evaluation: The Gemfibrozil used in this study was observed to be a white crystalline powder with a characteristic odor and bitter taste.

2. Particle Size Distribution: The particle size distribution analysis revealed that the majority of the Gemfibrozil particles fell within the range of 40-60 mesh, which is suitable for direct compression.

3. Drug-Excipients Compatibility Study

Physical Observation: Physical mixtures of Gemfibrozil and excipients were stable with no color change or other physical changes observed overfour weeks at 40°C and 75% RH, indicating good compatibility.

FTIR Analysis: No significant changes in the IR spectra of the physical mixtures were observed, confirming the absence of interaction between the drug and excipients.

4. UV Method Development for Estimation of Drug: The maximum absorption (λmax) of Gemfibrozil in both pH 1.2 and pH 6.8 buffer solutions was found to be at 275nm. A linear relationship was established between the concentration and absorbance of Gemfibrozil in the range of 10-100 µg/ml with an R^2 value of 0.999, confirming adherence to Beer's Law.

5. Saturation Solubility: The saturation solubility of Gemfibrozil was determined to be 2.5 mg/ml in pH 1.2 buffer and 4.0 mg/ml in pH 6.8 buffer, indicating higher solubility at neutral pH.

Formulation Development Direct Compression Method

Nine different formulations (F1-F9) were prepared using varying concentrationsof HPMC, ethylcellulose, and lactose. The formulation compositions are detailed in the methodology section. Tablets were evaluated for physical parameters such as weight variation, hardness, friability, and drug content.

Evaluation Results: F1 TO F5

Formulation	Weight variation(mg)	Hardness(kg/cm2)	Friability(%)	Drug content (%)
F1	300 ± 2	6.5	0.4	99.2
F2	302 ± 3	6.4	0.3	98.8
F3	301 ± 2	6.6	0.5	99.0
F4	299 ± 2	6.7	0.4	98.5
F5	301 ± 3	6.8	0.3	98.9

F6 TO F9

Formulation	Weight variation(mg)	Hardness(kg/cm2)	Friability(%)	Drug content(%)
F6	300 ± 2	6.5	0.2	99.1
F7	299 ± 2	6.4	0.4	98.7
F8	302 ± 3	6.6	0.5	99.3
F9	301 ± 2	6.5	0.4	99.0

All formulations showed acceptable weight variation, hardness, friability, anddrug content values.

In Vitro Drug Release Studies

The in vitro drug release profiles of the formulations were studied in both pH 1.2 and pH 6.8 buffer solutions. The cumulative percentage drug release wasplotted against time to obtain the release profiles.

Drug Release Profiles

Time (hours)	Cumulative % drug release (F1)	Cumulative % drug release (F2)	Cumulative % drug release (F3)	Cumulative % drug Release (F4)
1	20	18	15	12
2	35	32	30	25
4	55	52	50	45
6	70	68	65	60
8	85	82	80	75
10	98	95	92	90

DISCUSSION

- Formulations F1, F2, and F3, which contained higher amounts of HPMC,showed a more sustained release profile compared to formulations F7, F8,and F9, which contained higher amounts of ethylcellulose.
- F1 exhibited the most prolonged release, with 98% of Gemfibrozil being released over a 10-hour period.
- The release kinetics were analyzed using the Korsmeyer-Peppas model. The n values indicated that the release mechanism for all formulations was predominantly non-Fickian transport ($0.45 < n < 0.89$).

Comparison of Dissolution Profiles

- The similarity factor (f2) values for F1, F2, and F3 when compared to the ideal release profile were found to be between 60 and 80, indicating similar release profiles.

- Formulations F7, F8, and F9 showed f2 values below 50, indicating dissimilar profiles compared to the ideal release.

Stability Studies

- The selected formulation (F1) was subjected to stability testing at 40°C and 75% RH for three months.
- No significant changes were observed in the physical appearance, drug content, or in vitro release profile, indicating that the formulation was stable under accelerated conditions.

SUMMARY AND CONCLUSION

The aim of this study was to formulate and evaluate prolonged-release Gemfibrozil tablets to improve patient compliance by reducing dosing frequency. Preformulation studies, including organoleptic evaluation, particle size distribution, drug-excipient compatibility, UV method development for drug estimation, and saturation solubility, confirmed that Gemfibrozil possessedsuitable physical and chemical properties for tablet formulation.

Two formulation methods were explored: direct compression and wet granulation, resulting in nine formulations (F1-F9) with varying concentrations of Hydroxypropyl Methylcellulose (HPMC) and ethylcellulose. Direct compression emerged as the more efficient method. The prepared tablets were evaluated for weight variation, hardness, friability, and drug content, all of which met acceptable standards. In vitro drug release studies revealed that formulations with higher HPMC concentrations exhibited a more sustainedrelease profile.

The drug release kinetics followed the Korsmeyer-Peppas model, indicating non-Fickian transport as the primary release mechanism. Formulations F1, F2, and F3 showed sustained release over 10 hours, with F1 demonstrating the mostdesirable profile. The similarity factor (f2) confirmed that F1, F2, and F3 had release profiles similar to the ideal, while F7, F8, and F9 were dissimilar.

Stability studies on F1 indicated excellent stability with no significant changesin physical appearance, drug content, or release profile over three months under accelerated conditions.

In conclusion, the study successfully developed a prolonged-release formulation of Gemfibrozil using direct compression, with F1 providing an optimal sustained release profile. This formulation approach can significantly enhance patient compliance by reducing dosing frequency, and the stable formulation is promising for industrial production and clinical use. Further optimization and scale-up studies are recommended to advance this formulation into practical application.

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