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Formulation and Invitro Evaluation of Gemfibrozil Gastro Retentive Floating Tablet

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ABSTRACT

The purpose of present investigation was to develop and evaluate floating drug delivery system of an anti-hyperlipidemic agent. The floating tablets of Gemfibrozil were prepared by using Carbopol, Sodium alginate, Xanthan gum and HPMC K4M polymers. The pre-compression and post-compression evaluation were performed as per pharmacopeial standards. The tablets were prepared by direct compression method. Dissolution measurements were carried out in a (USP) dissolution testing apparatus II. Compatibility study was performed by FTIR. The compatibility study of the prepared Gemfibrozil floating tablets confirms that there is no interaction between the drug and polymers used. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms. The drug release kinetics was observed by super case II transport mechanism. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared Gemfibrozil floating tablet, it was concluded that the formulation F12 with Sodium alginate 80mg shows better sustained release effect i.e. the drug release was 99.08% at the end of 12^{th} hour. The release kinetic data implies that the release mechanism of all the formulations was super case II transport mechanism. The developed floating tablets of Gemfibrozil may be used to prolong drug release for at least 12h, thereby improving the bioavailability and patient compliance.

INTRODUCTION

GASTRORETENTIVE DRUG DELIVERY SYSTEM

Over the past 30 yrs., as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has focused on development of sustained or controlled release drug delivery system. Several reasons for attractiveness of the dosage form. It is recognized that for many diseased states, a substantial number of the therapeutic compound already exist. The effectiveness of this drug is limited by side effect of necessity to administer the compound in a clinical setting[1].

The goal in designing sustained and controlled release is to reduce frequency of dosing or increase effectiveness of the drug by localization at site of action, reducing dose frequency, providing uniform drug delivery[1]. The current controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years. However, this benefit had not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, or (iv) exhibit low solubilities at high pH values. These limits promoted the development of gastro retentive drug delivery systems (GRDDS). Besides being able to continually and sustainably deliver drugs to the small intestinal absorption window, the improvements provided from GRDDS include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora.

However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the drug delivery system (DDS) within desired regions of the gastrointestinal (GIT) and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable bio availability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Furthermore, the relatively brief GET (Gastric Emptying Time) in humans, which normally averages 2–3 h through the major absorption

zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GIT offers numerous advantages, especially for drugs exhibiting an absorption window in the GIT or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption[3].

From the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the GIT for a prolonged and predictable period of time exists today Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bio adhesive or mucoadhesive systems, high-density systems, super porous hydrogels and magnetic systems. The FDDS is one of the most leading methodologies in gastro retentive drug formulations[4].

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. The aim of the study was to design and evaluate floating drug delivery system of Gemfibrozil which may facilitate the following expectations.

❖ Improve the bioavailability of the drug.

❖ To increase the effectiveness in therapy.

❖ Reduction of dosing frequency.

❖ To improve patient compliance.

❖ To maintain plasma concentration of drug in therapeutic range for longer time.

The aim of the present study was to formulate and evaluate the FDDS of Gemfibrozil with following objectives.

- To formulate gastric floating tablet using excipients like Sodium alginate, Carbopol, Xanthan gum, PEO, $NaHCO_3$, etc for optimum deliver.
- To evaluate the powder mix for pre-compression characteristics and tablet characteristics.
- To evaluate physical properties like hardness, friability, density etc.
- To evaluate floating time of the formulation.
- To perform *in vitro* dissolution studies.

DRUG PROFILE & EXCIPIENT PROFILE

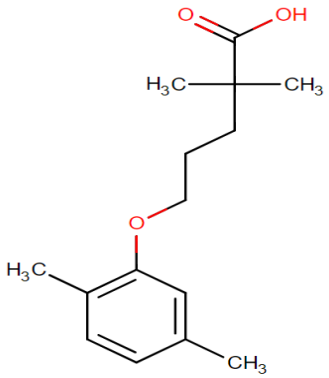
DRUG PROFILE:

Gemfibrozil:

Description:

Gemfibrozil is a lipid regulator that is used in the reduction of serum triglyceride levels in high-risk patients with hyperlipidemia.

Structure:



Structure of Gemfibrozil

IUPAC NAME:

5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid

CAS number: 25812-30-0

Chemical Formula: C15H22O3

Molecular weight:

Average: 250.3334

Monoisotopic: 250.15689457

PHARMACOLOGY:

Indication: Gemfibrozil is indicated to treat patients with Types IV and V hyperlipidemia who have elevated serum triglycerides (usually above 2000mg/dL), elevated VLDL cholesterol, fasting chylomicrons, are at risk of developing pancreatitis, and do not adequately respond to dietary restrictions.[11] Gemfibrozil is also indicated to reduce the risk of developing coronary heart disease in patients with Type IIb hyperlipidemia without history or symptoms of coronary heart disease; who do not adequately respond to weight loss, diet, exercise, and other medications; and have low HDL, raised LDL, and raised triglycerides.

Pharmacodynamics: Gemfibrozil alters lipid metabolism to treat patients with hyperlipidemia.[11] The duration of action requires twice daily dosing as the mean residence time of gemfibrozil is up to 9.6h in patients with chronic renal failure.[7] Gemfibrozil has a wide therapeutic index as trials with twice the standard dose were not associated with severe side effects.[8,11] Patients taking gemfibrozil may be at an increased risk of developing cholelithiasis and cholecystitis, as seen in patients taking clofibrate.

Mechanism of action: Gemfibrozil activates peroxisome proliferator-activated receptor-α (PPARα), which alters lipid metabolism. This activation leads to increased HDL, apo AI, apo AII, lipoprotein lipase (LPL), inhibition of apo B synthesis, peripheral lipolysis, decreased removal of free fatty acids by the liver, and increased clearance of ApoB. Upregulated LPL reduces plasma triglyceride levels. Decreased hepatic removal of fatty acids decreases the production of triglycerides. The effects on ApoB synthesis and

clearance decrease VLDL production which also reduce plasma triglyceride levels. Gemfibrozil's glucuronide metabolite is also an inhibitor of CYP2C8.

Half-life: Gemfibrozil's half-life is estimated to be around 2 hours.[7]

Protein binding: Gemfibrozil is 99% protein bound. It is 98.6% bound to serum albumin, 0.8% bound to erythrocytes, and 0.8% unbound. There is negligible binding to alpha-1-acid glycoprotein.

Volume of distribution: The volume of distribution of gemfibrozil is estimated to be 0.8L/kg.

Absorption: Gemfibrozil is absorbed from the gastrointestinal tract. In healthy volunteers, a 900mg oral dose of gemfibrozil has a C_{max} of 46±16µg/mL with a T_{max} of 2.2±1.1h.[7] In patients with chronic renal failure, gemfibrozil has a C_{max} of 13.8±11.1µg/mL with a T_{max} of 2.3±1.0h.[7] In patients with liver disease, gemfibrozil has a Cmax of 23.0±10.3µg/mL with a Tmax of 2.6±1.7h.

Metabolism:

Gemfibrozil undergoes hydroxylation at the 5'-methyl and 4' positions to form the M1 and M2 metabolites respectively. Gemfibrozil also undergoes O-glucuronidation to form gemfibrozil 1-beta glucuronide, an inhibitor of CYP2C8. This O-glucuronidation is primarily mediated by UGT2B7, but also by UGT1A1, UGT1A3, UGT1A9, UGT2B4, UGT2B17.

Elimination:

Approximately 70% of a dose of gemfibrozil is eliminated in the urine. The majority of a dose is eliminated as a glucuronide conjugate and <2% is eliminated as the unmetabolized drug 6% of a dose is eliminated in the faeces. In healthy volunteers, 0.02-0.15% of a dose was detected in the urine as unmetabolized gemfibrozil, with 7-14% detected as conjugated metabolites. In patients with renal failure, trace amounts of unmetabolized gemfibrozil is present in the urine, with 0.5-9.8% detected as conjugated metabolites. In patients with liver disease, 0.1-0.2% of a dose was detected in the urine as unmetabolized gemfibrozil, with 25-50% detected as conjugated metabolites.

List of Excipient used:

- Carbopol
- Sodium alginate
- Xanthan Gum
- Hydroxy Propyl methyl cellulose K4M
- Sodium Bicarbonate
- Magnesium Stearate
- Lactose
- Talc

MATERIALS AND METHODS

MATERIALS

Drugs & chemicals

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The double distilled water was used in all experiments.

Table 1: List of chemicals used with grade and supplier

S. no	Materials used	Grade	Manufacturer
1.	Gemfibrozil	Pharma grade	Manus Aktteva Biopharma LLP
2.	Sodium alginate	LR	Choice Organ chem LLP
3.	Carbopol 934P	LR	Neutron Drugs & Pharmaceuticals Pvt Ltd
4.	Xanthan gum	LR	Shreeji chemicals, Mumbai
5.	HPMC K 4M	LR	Shreeji chemicals, Mumbai
6.	Sodium bicarbonate	LR	S.D fine chemicals, Mumbai
7.	Lactose	LR	S.D fine chemicals, Mumbai
8.	Mg-Stearate	LR	Shreeji chemicals, Mumbai
9.	Talc	LR	Shreeji chemicals, Mumbai
10.	Hydrochloric acid	LR	Center drug house (p) Ltd, Mumbai

Instruments used for the preparation of Gemfibrozil tablets.

Table 2: List of instruments

S. No	Instrument	Manufacturer
1.	U.V. visible spectrophotometer	Shimadzu Corporation, Japan.
2.	FTIR spectrophotometer	IR-Affinity-1, Shimadzu, Japan.
3.	Electronic balance	Citizen scales Pvt. Ltd
4.	Digital pH meter	Digisun Electronics, Hyderabad
5.	Bulk density apparatus	Biological museum, Agra
6.	Tablet punching machine	Shakti, Ahmadabad
7.	Roche friabilator	Biological museum, Agra
8.	Tablet hardness tester	Pfizer
9.	Digital caliper	Aerospace
10.	USP dissolution XXIII apparatus	Electrolab TDL-08L
11.	Hot air oven	Universal

METHODS:

Pre formulation studies[9-13]

It is one of the important prerequisites in development of any drug delivery system. Preformulation studies of the drug were performed, which included melting point determination, solubility and compatibility studies.

- **Solubility studies:**

Solubility of Gemfibrozil was carried out in different solvents like- distilled water, 0.1 N HCL 7.4 pH & 6.8 pH buffers and organic solvents like Ethanol & Methanol. Solubility studies were performed by taking excess amount of drug in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using Whatman's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically.

- **Determination of melting point**

Melting point of Gemfibrozil was determined by capillary method. Fine powder of Gemfibrozil was filled in glass capillary tube (previously sealed on one end). The

capillary tube is tied to thermometer and placed in oil bath (light paraffin oil bath), The temperature at which it starts to melt was noted.

➢ **Determination of absorption maximum (λ_{max}):**

The wavelength at which maximum absorption of radiation takes place is called as λ_{max}. This λ_{max} is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 10mg Gemfibrozil separately was dissolved in 2-3 ml of methanol in a clean 10ml volumetric flask. The volume was made up to 10ml with 0.1N HCL buffer which will give stock solution-I with concentration 1000µg/ml. From the stock solution-I, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 0.1N HCL buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 0.1N HCL buffer to get a concentration of 10µg/ml. This solution was then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ-max).

➢ **Construction of calibration curve:**

Accurately weighed 10mg Gemfibrozil was dissolved in methanol taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 0.1N HCL buffer which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 0.1N HCL buffer to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 0.1N HCL buffer to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 278.0 nm.

➢ **Compatibility**

➢ **FTIR**

Compatibility studies were performed through FTIR spectroscopy. The IR spectrum

of pure drug and physical mixture of drug and polymer was studied. The characteristic absorption peaks of Gemfibrozil obtained were obtained at 4000-500cm^{-1}. It has been observed that there is no chemical interaction between Gemfibrozil and polymers used. From the fig no 5.3, 5.4, 5.5, 5.6, & 5.7 it was observed that peak obtained in spectra drug a polymer. which show there were no interaction between drug and polymers.

Pre-compression evaluation[14-15]

Angle of Repose

Angle of repose was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula.

$$\emptyset = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Table 3: Angle of Repose (ɵ) properties

Angle of Repose (ɵ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
<40	Very poor

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (*Vb*) and weight of powder (*M*) was determined. The bulk density was calculated using the formula.

$$\rho b = \frac{m}{Vd}$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (*Vt*) occupied in the cylinder and weight (M) of the blend was

measured. The tapped density (*ρb*) was calculated using the following formula.

$$pt = \frac{m}{Vt}$$

Carr's compressibility index

The simplest way of 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. The compressibility index of the granules was determined by Carr's compressibility index, which is calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

Table 4: % Compressibility properties

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Haunser ratio} = \frac{pt}{pd}$$

Where ρt is tapped density and ρd is bulk density. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

Preparation of Gemfibrozil floating tablets

By direct compression method

Gemfibrozil floating was prepared by direct compression technique using drug and

variable concentration of polymers (Carbopol 934P, Sodium alginate, Xanthan gum, HPMC K4M, Sodium Bicarbonate, Lactose, Mg-stearate, and Talc). The respective powders & optional additives (composition listed in table-5.3) were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

COMPOSITION OF GEMFIBROZIL FLOATING TABLETS

Table 5: Composition of Gemfibrozil floating tablet with FLT and TFT

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Gemfibrozil	160	160	160	160	160	160	160	160	160	160	160	**160**
HPMC K 4M	120	100	80	-	-	-	-	-	-	-	-	**-**
Carbopol	-	-	-	120	100	80	-	-	-	-	-	**-**
Xanthan gum	-	-	-	-	-	-	120	100	80	-	-	**-**
Sodium alginate	-	-	-	-	-	-	-	-	-	120	100	**80**
NAHCO3	20	20	20	20	20	20	20	20	20	20	20	**20**
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	**2**
Talc	3	3	3	3	3	3	3	3	3	3	3	**3**
Lactose	95	115	135	95	115	135	95	115	135	95	115	**135**
Total	400	400	400	400	400	400	400	400	400	400	400	**400**
FLT(Seconds)	112	102	95	85	63	56	120	102	91	98	65	**49**
TFT (hrs)	>12	>12	12	>12	>12	>12	>12	>12	12	>12	>12	**>12**

Post-compression evaluation parameters for formulated tablets [16-19]

a. Weight variation

Twenty tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight.

b. Hardness

The hardness of the tablet from each formulation was determined using Pfizer hardness tester.

c. Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$\textbf{Friability (f)} = \left(1 - \frac{W_0}{W}\right) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test.

d. Thickness and diameter

The thickness and diameter of tablet was carried out using Digital caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

e. Drug content

Powder one tablets extraction was carried out using 0.1 N HCL. The concentration was determined spectrophotometrically against appropriate blank. Calculate the content of Gemfibrozil specific absorbance at 278 nm. As given in IP.

f. *In-vitro* buoyancy studies

The in vitro floating behavior of the tablets was studied by placing them in 100 ml beaker 100 ml of 0.1 N HCl (pH 1.2, 37 ^{0}C). The time, tablet required for the emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT). And the time tablet constantly float on the surface of the medium is called total floating time (TFT).

g. *In-vitro* dissolution studies

The release rate of Gemfibrozil from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.5^0C and 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium.

Kinetic Analysis of In-Vitro Release Rates of Gastro Retentive Tablets[20-21]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

- **Zero Order Kinetic**

It describes the system in which the drug release rate is independent of its concentration.

$$Qt = Qo + Ko\ t$$

Where

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero and

Ko = zero order release constant.

If the zero-order drug release kinetic is obeyed, then a plot of Qt versus t will give a straight line with a slope of Ko and an intercept at zero.

- **First Order Kinetic**

It describes the drug release from the systems in which the release rate is concentration

dependent.

$$\textbf{Log Qt = log Qo + kt/ 2.303}$$

Where

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution k = first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt) versus t will be straight line with a slope of kt/ 2.303 and an intercept at t=0 of log Qo.

- **Higuchi Model**

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$\textbf{Mt / M}\infty\textbf{= kHt}^{1/2}$$

Where

Mt and M∞ are cumulative amounts of drug release at time t and infinite time, And

kH = Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot of Mt / M∞ versus $\mathbf{t}^{1/2}$ will be straight line with slope of kH.

- **Korsmeyer-Peppas model (Power Law)**

The power law describes the drug release from the polymeric system in which release deviates.

from Fickian diffusion, as expressed in following equation.

$$\textbf{Mt / M}\infty\textbf{= ktn}$$

$$\textbf{log [Mt / M}\infty\textbf{] = log k + n log t}$$

Where

Mt and M∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction

of drug release at time t),

device, **k =** constant incorporating structural and geometrical characteristics of CR

n = diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

To characterize the release mechanism, the dissolution data {Mt / M∞ <0.6} are evaluated.

A plot of log {Mt / M∞} versus log t will be linear with slope of n and intercept gives the value of log k.

Antilog of log k gives the value of k.

Peepas used the n value in order to characterize different release mechanisms as shown in the table below.

RESULTS:

PREFORMULATION STUDIES

Determination of melting point

The melting point of Gemfibrozil was found to be in range of 58°–61°C.

Determination of Solubility

Buffers	**Solubility(µg/ml)**
0.1N HCL	0.896
6.8pH Phosphate Buffer	0.654
7.4 pH Phosphate Buffer	0.568

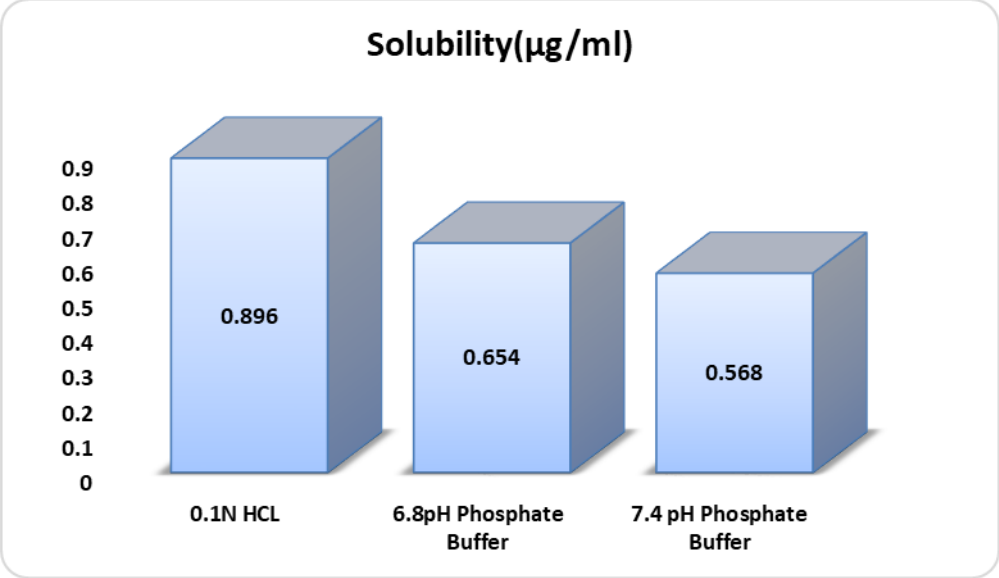


Fig 1: Solubility studies of pure drug

DISCUSSION:

From the above obtained solubility studies, we can say solubility of the drug is more in 0.1N HCL than the other buffers.

ESTIMATION OF GEMFIBROZIL BY UV SPECTROSCOPY

Determination of lambda max

UV Spectra of Gemfibrozil at 4 µg/ml concentration the Wavelength of maximum absorption in 0.1N HCL solution was found to be 278.0 nm**.**

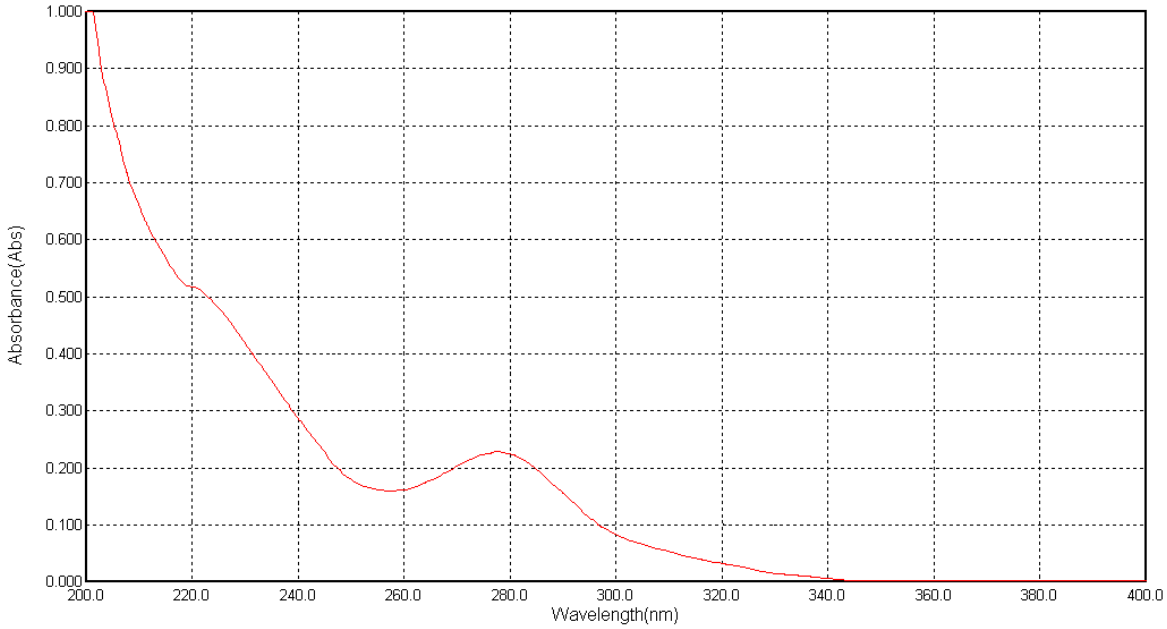


Fig 2: UV SPECTRUM OF GEMFIBROZIL

Discussion: The maximum absorbance of the Gemfibrozil in 0.1N HCL was found to be 278 nm for 50% concentration solution as shown in Fig. Hence, the wavelength of 278 nm was selected for analysis of drug in dissolution media.

Calibration curve

Table 6: Absorbance data for the calibration curve of Gemfibrozil in 0.1N HCL

Concentration(µg/ml)	Absorbance
0	0
2	0.131
4	0.236
6	0.352
8	0.452
10	0.562
12	0.675

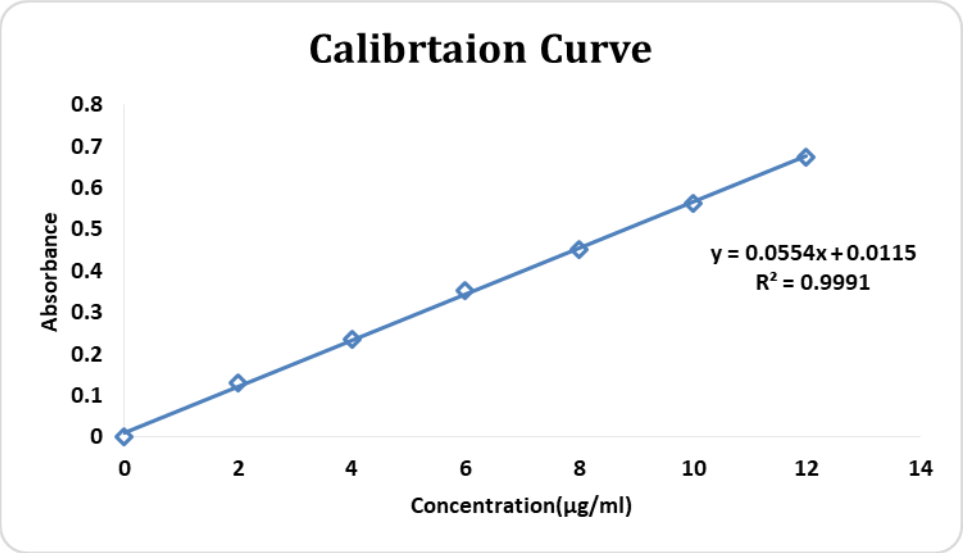


Fig 3: Standard calibration curve of Gemfibrozil in 0.1N HCl

Discussion:

The linearity was found to be in the range of 2-12µg/ml in 0.1 N HCl. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

COMPATABILITY STUDIES

FTIR Spectroscopy

Identification of Gemfibrozil

The IR spectrum of pure drug was found to be similar to the standard spectrum of Gemfibrozil. The spectrum of Gemfibrozil shows the following functional groups at their frequencies shown in table 3.

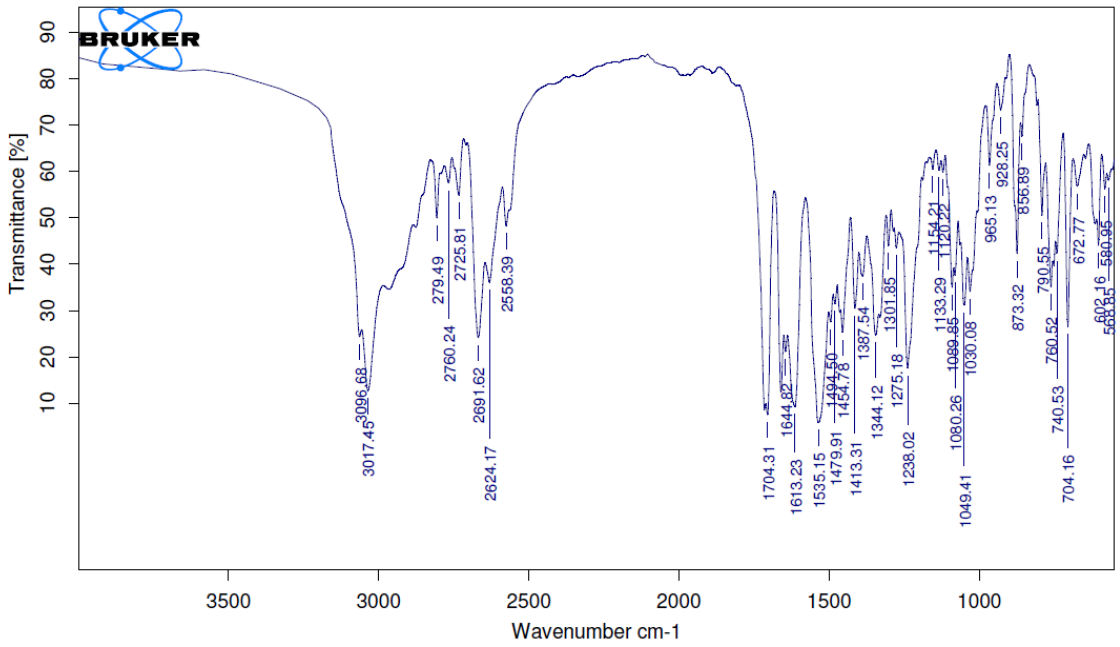


Fig 4: IR spectra of Gemfibrozil.

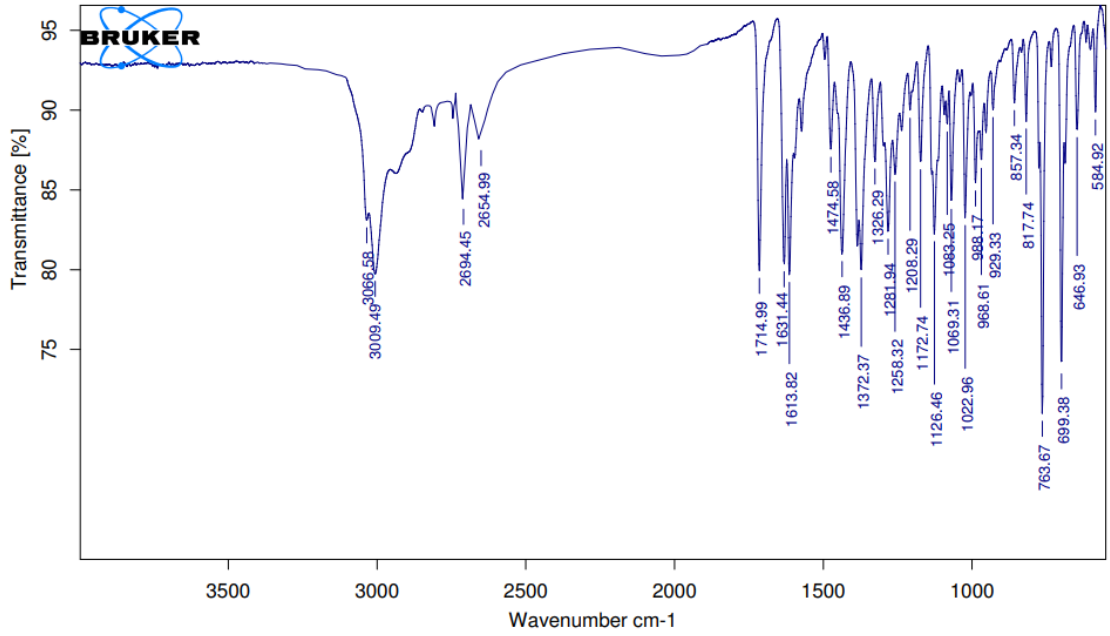


Fig 5: FT-IR Spectra of Gemfibrozil best formulation.

Discussion:

From the compatibility studies it was concluded that the functional groups that were present in the pure drug were also found in the optimized formulation with very minute changes, from this we can conclude that the drug and excipients have no interactions.

PRE-COMPRESSION EVALUATION OF GEMFIBROZIL FLOATING TABLETS

Table 7: pre-compression parameters of Gemfibrozil floating tablets

Formulation code	Angle of repose (θ) ±SD	Bulk density (gm/cm)	Tapped density	Hausner ratio (HR)±SD	Carr index (CI) ±SD
F1	24.43±0.18	0.378±0.015	0.447±0.018	1.24±0.018	17.48±0.58
F2	26.14±0.75	0.385±0.042	0.464±0.025	1.19±0.024	15.72±0.94
F3	27.12±0.19	0.398±0.026	0.485±0.046	1.16±0.015	14.17±0.25
F4	28.75±0.38	0.415±0.031	0.497±0.028	1.14±0.019	13.24±0.47
F5	25.36±0.45	0.368±0.015	0.456±0.042	1.22±0.024	18.48±0.46
F6	26.86±0.37	0.397±0.019	0.468±0.019	1.18±0.012	17.21±0.14
F7	27.18±0.49	0.405±0.010	0.485±0.045	1.16±0.015	15.36±0.47
F8	28.57±0.85	0.418±0.011	0.499±0.018	1.13±0.019	14.08±0.28
F9	26.25±0.68	0.384±0.005	0.468±0.013	1.17±0.014	16.24±0.48
F10	27.64±0.84	0.395±0.010	0.475±0.009	1.15±0.023	14.04±0.29
F11	28.48±0.45	0.418±0.010	0.496±0.022	1.13±0.015	13.28±0.46
F12	29.85±0.28	0.426±0.011	0.514±0.027	1.10±0.034	11.12±0.18

All the values are expressed as mean ± SD. (n=1)

Discussion: The angle of repose of different formulations was ≤ 29.85±0.28% which indicates that material had good flow property. So, it was confirmed that the flow property of blends was free flowing. The bulk density of blend was found between 0.378±0.015g/cm^3 to 0.426±0.011 g/cm^3.Tapped density was found between 0.447±0.018 g/cm^3 to 0.514±0.027 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.12±0.18-18.48±0.46. and Hausner's ratio from 1.10±0.034-1.24±0.018 which reveals that the blends have good flow characterization.

POST COMPRESSION EVALUATION OF GEMFIBROZIL FLOATING TABLETS

Table 8: Post-compression evaluation of Gemfibrozil floating tablets

Formulation code	Weight variation Average wt in (mg)±SD	Hardness (Kg/cm^2) ±SD	Diameter in (mm) ±SD	Thickness in (mm) ±SD	Friability (%) ±SD	Drug content uniformity (%) ±SD
F1	400.25± 0.17	5.37± 0.41	8.27± 0.57	3.42± 0.08	0.78± 0.09	97.48±0.48
F2	403.78± 0.28	5.25± 0.28	8.45± 0.57	3.28± 0.07	0.66± 0.07	96.75±0.28
F3	398.69± 0.64	5.14± 0.41	8.14± 0.57	3.19± 0.09	0.54± 0.06	95.15±0.46
F4	399.87± 0.18	5.14± 0.62	8.15± 0.0	3.21± 0.06	0.43± 0.05	96.32±0.47
F5	400.45±0.28	5.36± 0.84	8.24± 0.57	3.45± 0.04	0.86± 0.08	98.52±0.65
F6	400.28± 0.46	5.78± 0.45	8.26± 0.57	3.26± 0.06	0.72± 0.05	97.48±0.45
F7	397.45± 0.54	5.28± 0.25	8.15± 0.00	3.19± 0.07	0.76± 0.05	98.78±0.28
F8	399.48± 0.18	5.24± 0.68	8.36± 0.57	3.49± 0.08	0.59± 0.08	96.18±0.18
F9	398.85± 0.46	5.58± 0.97	8.35± 0.57	3.26± 0.08	0.66± 0.05	97.44±0.36
F10	401.47± 0.85	5.45± 0.41	8.45± 0.57	3.45± 0.05	0.57± 0.05	98.42±0.21
F11	402.19± 0.51	5.96± 0.28	8.15± 0.25	3.45± 0.06	0.48± 0.07	98.53±0.25
F12	400.18± 0.95	5.98± 0.20	8.56± 0.57	3.65± 0.07	0.89± 0.06	98.86±0.41

All the values are expressed as mean ± SD. (n=3)

Discussions:

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (F1 to F12) tablets passed weight variation test as the % weight variation was within the pharmacopeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of all the formulations ranged between 5.14± 0.41-5.98± 0.20 kg/cm2. This ensures good handling characteristics of all batches.

Thickness and Diameter: The measured Thickness and Diameter of tablets of all the

formulations ranged between 3.19± 0.07-3.65± 0.07 mm and 8.14± 0.57-8.56± 0.57mm.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

The Drug Content: The Content of drug content for F1 to F12 was found to be between 95.15±0.46% - 98.86±0.41%. It complies with official specifications.

***IN-VITRO* DRUG RELEASE STUDIES**

***In-vitro* drug release data of Gemfibrozil floating tablets**

Table 9: *In-vitro* drug release data of Gemfibrozil floating tablets of Batch F1 to F6

#All the values are expressed as mean ± SD.(n=1)

% Cumulative release						
Time (Hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	8.48%	15.23%	19.45%	14.62%	15.58%	17.32%
2	15.84%	27.48%	25.84%	23.44%	18.26%	23.33%
3	21.56%	32.85%	34.18%	29.75%	24.18%	28.77%
4	29.64%	40.18%	45.62%	33.94%	37.48%	38.45%
5	36.45%	49.65%	51.21%	38.74%	43.63%	49.71%
6	42.21%	57.32%	59.57%	46.83%	57.21%	58.58%
7	49.62%	62.85%	65.48%	55.86%	64.28%	69.47%
8	57.26%	69.45%	71.28%	67.48%	75.48%	72.42%
9	63.84%	76.12%	79.64%	72.38%	81.24%	78.56%
10	79.25%	83.24%	85.26%	79.48%	89.48%	83.38%
11	85.68%	89.64%	90.24%	85.39%	93.48%	87.48%
12	93.45%	95.24%	97.65%	95.73%	96.64%	97.35%

Table 10: *In-vitro* drug release data of Gemfibrozil floating tablets of Batch F7 to F12

All the values are expressed as mean ± SD. (n=3)

% Cumulative release						
Time (Hrs)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0
1	10.27%	14.24%	18.89%	15.04%	18.05%	**24.98**%
2	16.47%	19.66%	24.32%	18.91%	24.95%	**32.95**%
3	21.48%	24.21%	29.62%	27.64%	28.27%	**39.83**%
4	28.75%	29.35%	32.41%	34.47%	36.11%	**43.82**%
5	35.83%	35.39%	37.37%	38.55%	48.03%	**55.77**%
6	39.96%	42.85%	42.65%	50.08%	52.94%	**62.48**%
7	49.11%	49.70%	49.87%	57.03%	56.63%	**69.42**%
8	53.98%	52.92%	56.51%	66.11%	68.26%	**75.42**%
9	59.64%	58.63%	67.51%	69.34%	74.87%	**79.99**%
10	71.46%	66.23%	74.09%	75.40%	85.94%	**88.37**%
11	79.26%	83.73%	82.86%	84.95%	88.73%	**95.33**%
12	92.36%	94.81%	95.62%	90.81%	93.54	**99.08**%

Discussion:

From the in vitro drug release in studies, it was observed that the formulations containing Sodium alginate as a polymer in different concentrations like 120mg, 100mg and 80mg, reveals that the decreased in the polymer concentration increases the drug release time and the F12 formulation containing Sodium alginate 80 mg concentration shows maximum amount of drug release (**99.08**%) at the end of 12 hours.

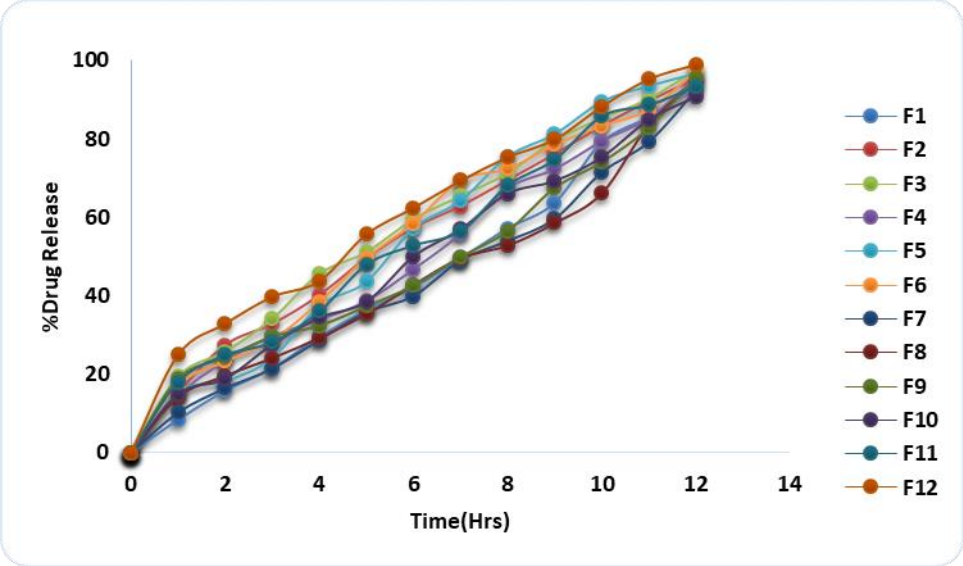


Fig 6: *In-vitro* drug release profile of Gemfibrozil floating tablets of batches F1 to F12

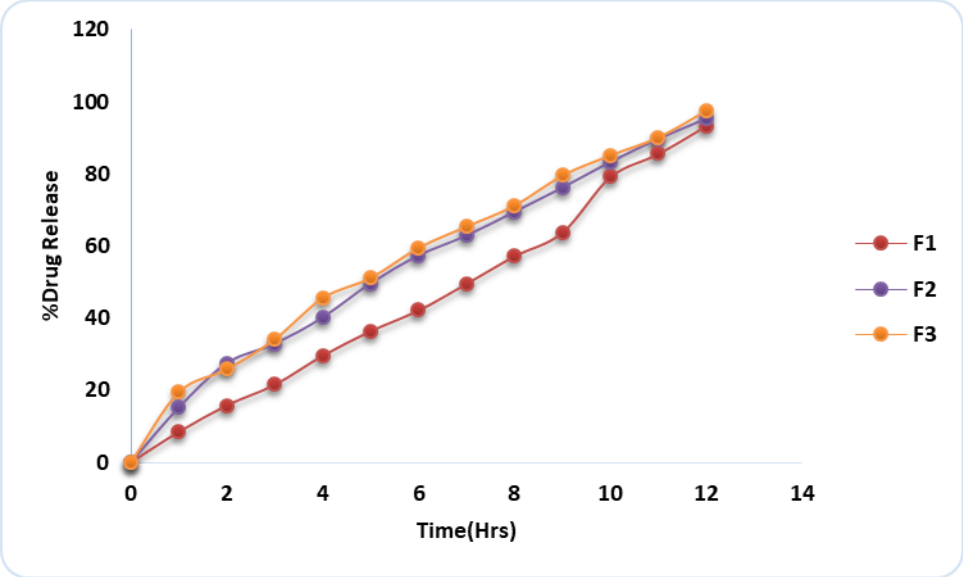


Fig 7: *In-vitro* drug release profile of Gemfibrozil floating tablets of batches F1 to F4

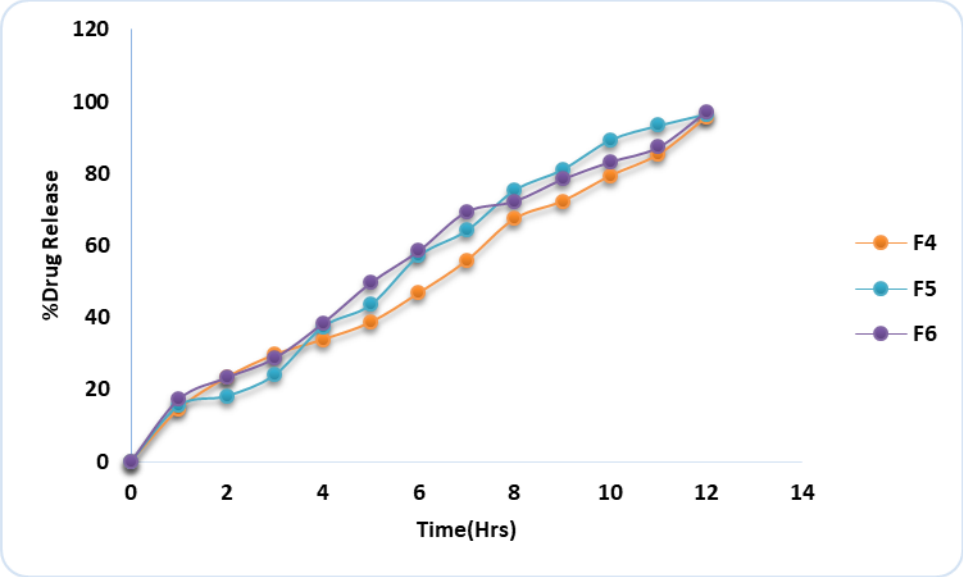


Fig 8: *In-vitro* drug release profile of Gemfibrozil floating tablets of batches F4 to F8

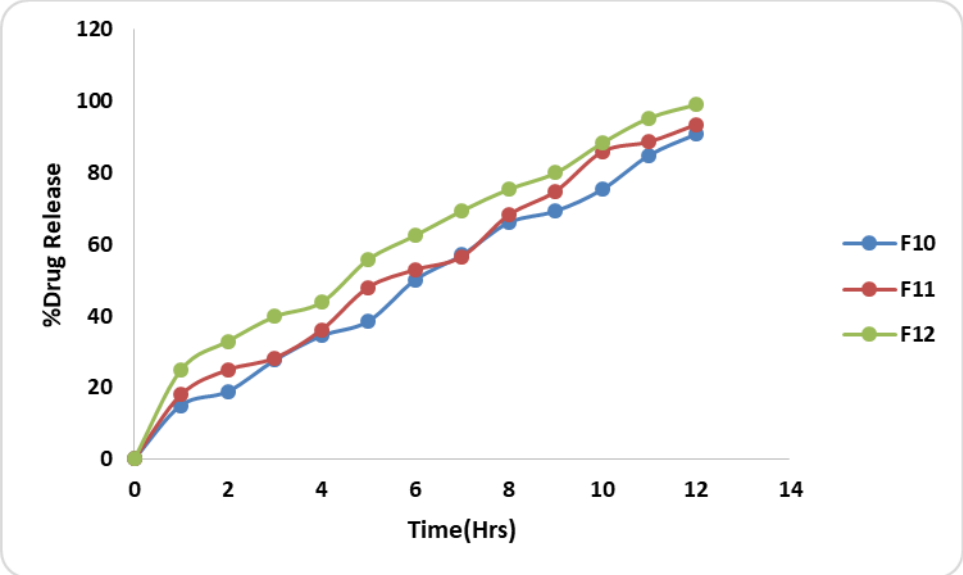


Fig 9: *In-vitro* drug release profile of Gemfibrozil floating tablets of batches F9 to F12

Drug release kinetics:

Zero Order Release Studies for Optimized Formulation:

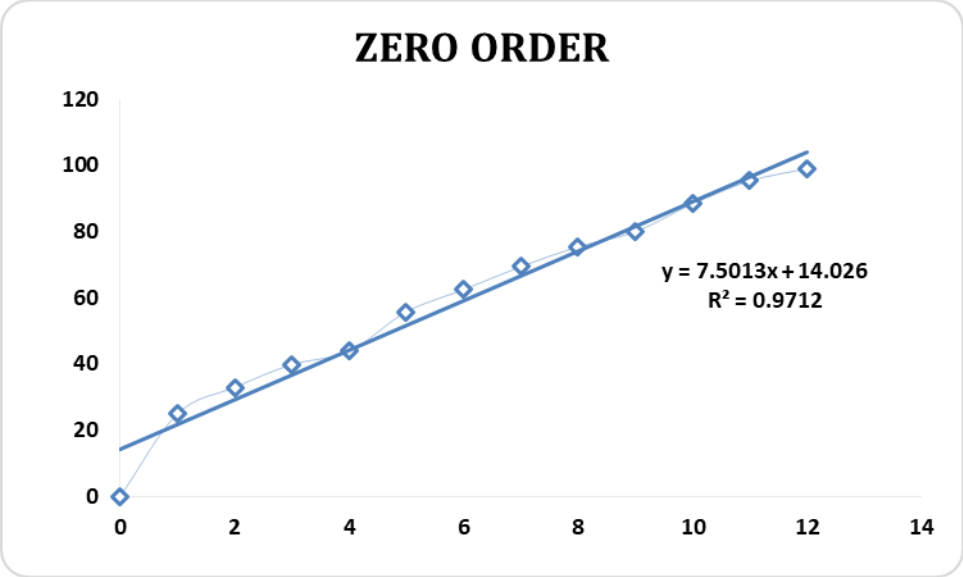


Fig 10: Zero Order

First Order Release Studies for Optimized Formulation:

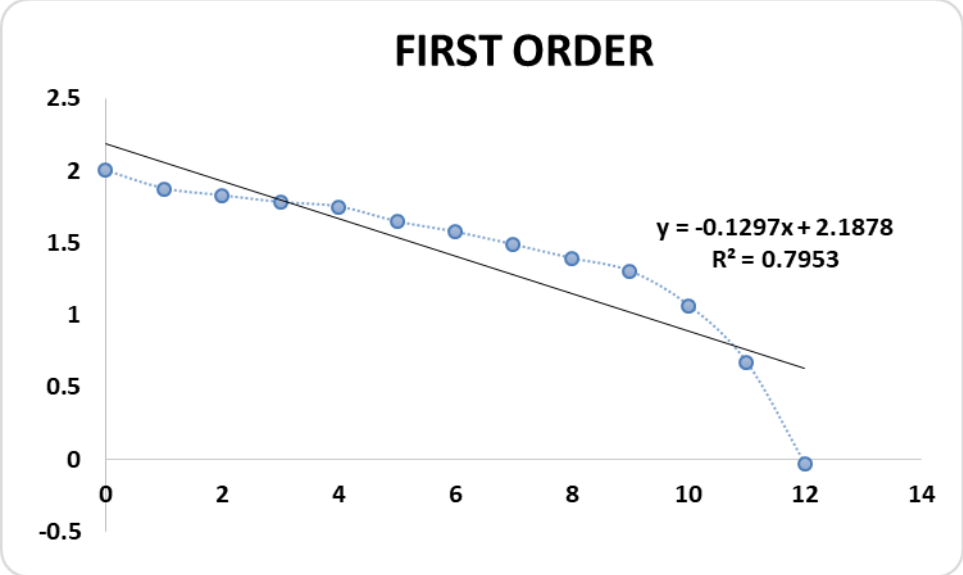


Fig 11: First Order

Higuchi Plot Release Studies for Optimized Formulation:

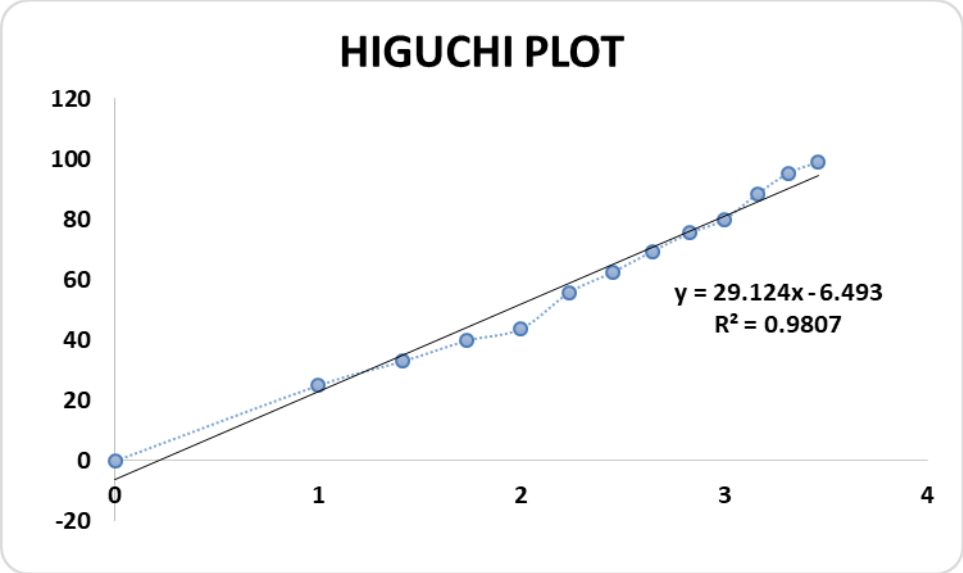


Fig 12: Higuchi

Peppa's Plot Release Studies for Optimized Formulation:

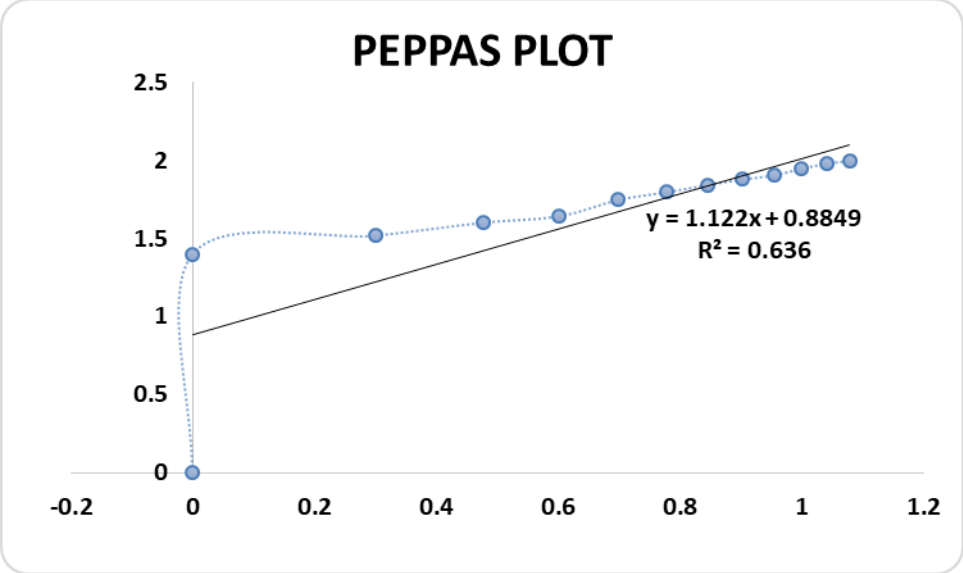


Fig 13: Peppas Plot

Discussion: The *in-vitro* drug release data was subjected to analysis according to zero order, first order kinetic equations,

Higuchi and Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis of data including regression coefficient are summarized.

When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' values of zero order were in the range of 0.971 whereas the 'r' values of first order plots were found to be in the range of 0.795 indicating drug release from all the formulations were found to follow zero order kinetics.

The Higuchi's plot has shown with the regression values in the range of 0.980.

The Peppas plot has shown with the regression values in the range of 0.636.

The *in-vitro* dissolution data as log cum percent drug release versus log time were fitted to Peppas, values of the exponent 'n' was found to be in the range of 1.122 indicating that the drug release follows super case II transport mechanism and zero order release.

SUMMARY

The present study is an attempt to develop floating tablets of Gemfibrozil, with different polymers which releases a therapeutic amount of Gemfibrozil to the proper site in the body and also to achieve and maintain the desired Gemfibrozil concentration.

Direct compression method was used for formulation of floating tablets, also different types of polymers like Carbopol, Sodium alginate, Xanthan gum and HPMC K 4M were studied. These polymers were widely used gel forming polymers. The release rate could effectively be modified by varying the "polymer" concentration. By using Sodium alginate, they gave optimum FLT as well as long acting effect. It was found that the tablet formulation retarded the drug release for 12h as desired.

The results of the drug-excipients compatibility by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. The Pre compression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. The final formulation showed acceptable flow properties. The post compression parameters like the thickness, hardness, friability, weight variation, content uniformity, FLT and TFT and *In vitro* release, were carried out and the values were found to be within IP limits.

Thus it is summarized and concluded that Sodium alginate with 80mg can be successfully used in formulation of Gemfibrozil sustained release gastro retentive floating tablets which show the release of 99.08% at the end of 12^{th} hour.

CONCLUSION

From the compatibility studies, it is concluded that, Carbopol, Sodium alginate, Xanthan gum and HPMC K4M, were compatible with drug Gemfibrozil and thus suitable for the formulation of Gemfibrozil floating tablets were fabricated by direct compression method.

In-vitro buoyancy studies were performed for all the formulations, F1 to F12 by using 0.1 N HCL solution at 37^0C. Tablet containing Sodium Alginate (F12) showed good buoyancy with very short lag time and long floatation time of more than 12 hrs in 0.1 N HCL. *In-Vitro* release study is performed for 12 hrs. Optimized formula containing Sodium alginate (F6) showed better release compare to other formulations and it followed zero order kinetics. The super case II transport mechanism was confirmed as the drug release mechanism from this formulation.

From this study, it was concluded that Sodium alginate can be used in formulation of Gemfibrozil sustained release gastro retentive floating drug delivery system. Overall, this study concludes that viscosity of the polymer is a major factor affecting the drug release and floating properties of FDDS.

SCOPE FOR THE FUTURE STUDIES

■ The principle of FDDS can be adopted for drug acting locally in stomach.

■ The work can be extended to the In-vivo studies to conclude In-vitro and In- vivo correlation Work can be extended to the In-vivo buoyancy studies in humans.

■ The formulation of FDDS can be tried with different grades of Sodium Alginate and other swellable polymers.

■ The work can be carried out to study the effect of other response parameters like bio adhesiveness, etc, on floating and release rate of drug.

■ The work can be carried out to improve the physical stability of the dosage form like coating the tablet.

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