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FORMULATION AND EVALUATION OF GASTRORETENTIVE TABLETS CONTAINING GEMFIBROZIL

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ABSTRACT

Gemfibrozil is used along with a proper diet to help lower fats (triglycerides) and raise "good" cholesterol (HDL) in the blood. Floating gastro retentive tablets containing Gemfibrozil were prepared using direct compression method. Total nine formulations were prepared using varying amount of HPMC-K4 and HPMC-K15. The prepared Tablets were further evaluated for Hardness, Friability, floating behavior, and uniformity of drug content, and *In-vitro* Release Studies. Percentage assay of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 95.58±0.54-98.96±0.65%. The maximum percentage buoyancy and floating lag time was found to be formulation F7 in gastro retentive tablets. The optimized formulation of batches subjected to further studies. When the regression coefficient values of were compared, it was observed that 'r' values of First order was maximum *i.e.* 0.990 hence indicating drug release from formulations was found to follow First order Hixson-Crowell release kinetics. The in vitro dissolution studies showed that Gemfibrozil tablets formulation F7 showed better sustained effect over a period of 12 hours than floating formulations.

Key words: Gemfibrozil, sustain release, floating, tablets, evaluation, In vitro drug release.

INTRODUCTION

Floating systems or dynamically controlled systems are low-density systems that have sufficiently 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 [1]. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration [2-3]. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

Oral route is the most commonly adopted and convenient route for drug delivery because of flexibility in the formulation, patient compliance and physician's convenience for dose adjustment. Most of the conventional dosage formulations are immediate-release systems where there is no control over drug release and often results in multiple dosing that lead to fluctuations in plasma drug concentration [4-5].

One of the most common approach used for prolonging and controlling the rate of drug release is incorporating the drug in a hydrophilic colloidal such as Hydroxypropyl methyl cellulose, Hydroxypropyl cellulose, carbopols, chitosan, alginates and gelatin etc [6].

Major drawback associated with conventional drug poor patient compliance: Chances of missing of the dose of a drug. The unavoidable fluctuations of drug concentration may lead to under medication or over medication. A typical peak valley plasma concentration time profile is obtained which makes attainment of drawback of conventional dosage form. The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur. To overcome the problem associated with conventional drugs Present investigation deals with formulation development and evaluation of gastro retentive sustain release tablets of antidepressant drugs [7.8].

MATERIALS AND METHODS

Materials

A gift sample of Gemfibrozil received from Bioplus Life Science, Bangalore; PVP (S. D. Fine Chem.

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Ltd., Mumbai), Citric acid (Qualigens fine chemicals, Mumbai), HPMC (Ozone international, Mumbai) and others chemicals used were analytical grade.

Method for Preparation of Gemfibrozil Floating Tablet

Direct compression was taken after to manufacture the gas generating floating tablets of Gemfibrozil. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan.

Excipients like sodium bicarbonate, citrus extract anhydrous, magnesium stearate were selected for the examination. Sodium bicarbonate and citrus extract were utilized as gas creating specialist. Citrus extract was additionally utilized as an antioxidant. Steps associated with the manufacture of tablets, first the medication; polymer and different excipients selected were gone through 40 mesh sieve. Required amount of medication, polymer and excipients were weighed legitimately and moved into polyethylene pack and the mix was blended for no less than 15 min. The mix acquired was then lubricated by including 1% magnesium stearate and again blended for another 5 min.

EVALUATION OF TABLETS

Bulk Density

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all Preformulation lots is necessary to avoid misleading predictions [9,10].

Tapped Density

Tapped density is determined by measuring the volume of a known mass of powder sample before and after the tapping that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup [11].

Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material [12].

Hausner ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density [13].

Hausner ratio = Tapped density / Bulk Density

***In vitro* Buoyancy Studies**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time [13].

Dissolution Rate Studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Gemfibrozil tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10 ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 278.0 nm using spectroscopy.

Table 1. Various Formulations of Gemfibrozil Gastro Retentive Tablets

Excipients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Gemfibrozil	300	300	300	300	300	300	300	300	300
HPMC K15	80	100	120	-	-	-	40	50	60
HPMC K4	-	-	-	80	100	120	40	50	60
PVP K30	20	20	20	20	20	20	20	20	20
Citric Acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	65	45	25	65	45	25	65	45	25
Total Weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

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Table 2. Result of Pre-Compression Properties of Gemfibrozil FGR Tablets

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner Ratio
F1	0.395	0.425	7.059	1.076
F2	0.389	0.432	9.954	1.111
F3	0.385	0.421	8.551	1.094
F4	0.387	0.412	6.068	1.065
F5	0.38	0.452	15.929	1.189
F6	0.378	0.426	11.268	1.127
F7	0.374	0.425	12.000	1.136
F8	0.379	0.436	13.073	1.150
F9	0376	0.421	10.689	1.120

Table 3. Results of Post Compression Properties of Gemfibrozil FGR tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	4.20	4.5	502±8	0.852	98.65±0.23	MT 12
F2	4.25	4.3	505±7	0.895	95.58±0.54	MT 12
F3	4.32	4.2	512±9	0.852	96.65±0.41	MT 12
F4	4.20	4.5	502±6	0.874	98.78±0.25	MT 12
F5	4.23	4.6	506±5	0.895	98.96±0.65	MT 12
F6	4.32	4.5	504±8	0.865	99.45±0.41	MT 12
F7	4.32	4.7	508±12	0.745	98.78±0.65	MT 12
F8	4.25	4.8	508±9	0.745	98.74±0.74	MT 12
F9	4.12	4.5	507±7	0.658	98.85±0.32	MT 12

Table 4. Results of *In-Vitro* Buoyancy Study of Gemfibrozil FGR Floating time

Formulation Code	Floating Lag Times (Sec)
F1	35
F2	36
F3	45
F4	48
F5	45
F6	56
F7	30
F8	38
F9	34

Table 5. *In-vitro* drug release study of GRF tablets.

Time (hr)	% Cumulative Drug Release								
CODE	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.5	36.65	34.85	32.56	28.98	24.45	22.23	20.14	18.98	15.69
1	55.42	53.12	49.95	45.58	38.89	35.65	30.56	25.65	23.14
1.5	65.58	60.25	65.52	60.23	55.45	48.89	42.25	35.65	30.14
2	89.98	85.45	79.89	73.21	69.98	55.47	50.65	45.56	42.25
3	98.12	98.65	85.65	80.25	78.38	75.65	65.58	50.23	48.98
4	-	-	96.45	92.23	89.78	89.98	73.32	65.47	55.65
6	-	-	-	97.89	98.78	95.56	88.98	79.98	69.98
8	-	-	-	-	-	98.78	96.65	88.21	73.36
12	-	-	-	-	-	-	98.89	93.23	82.23

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Table 6. *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)1/2	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	20.14	1.304	79.86	1.902
1	1	0	30.56	1.485	69.44	1.842
1.5	1.225	0.176	42.25	1.626	57.75	1.762
2	1.414	0.301	50.65	1.705	49.35	1.693
3	1.732	0.477	65.58	1.817	34.42	1.537
4	2	0.602	73.32	1.865	26.68	1.426
6	2.449	0.778	88.98	1.949	11.02	1.042
8	2.828	0.903	96.65	1.985	3.35	0.525
12	3.464	1.079	98.89	1.995	1.11	0.045

Figure 1 *In-vitro* drug release study of GRF tablets.

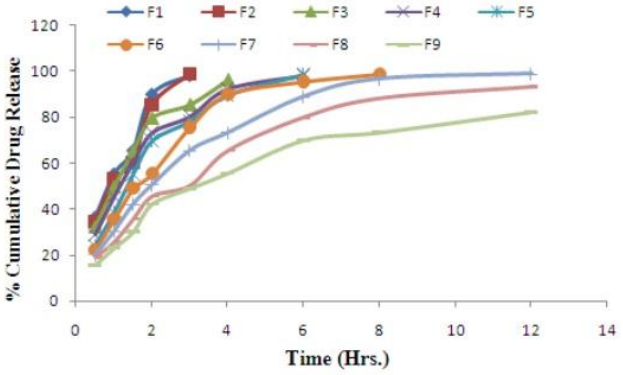


Figure 2 Zero order release Kinetics (Cumulative % drug released Vs Time)

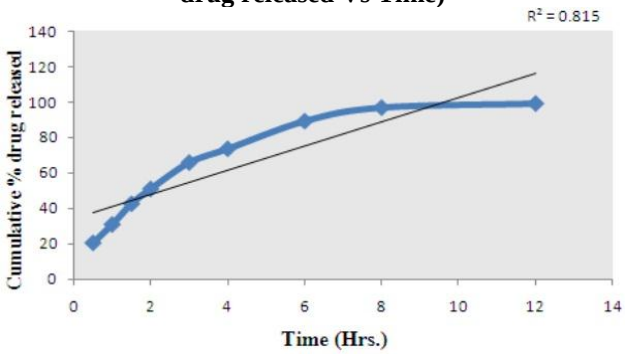


Figure 3 First order release kinetics (Log cumulative % drug remaining Vs Time)

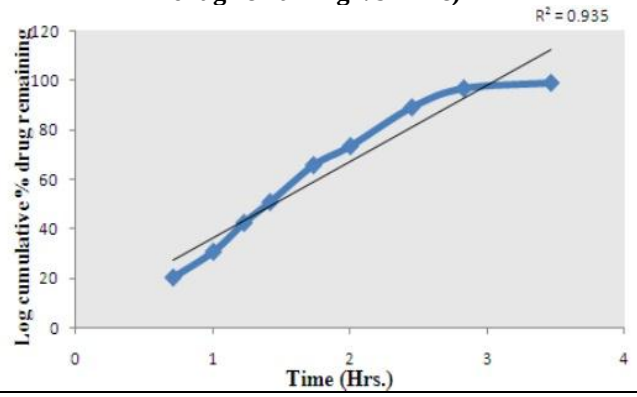


Figure 4 Higuchi release Kinetics (Cumulative % drug released Vs Root Time)

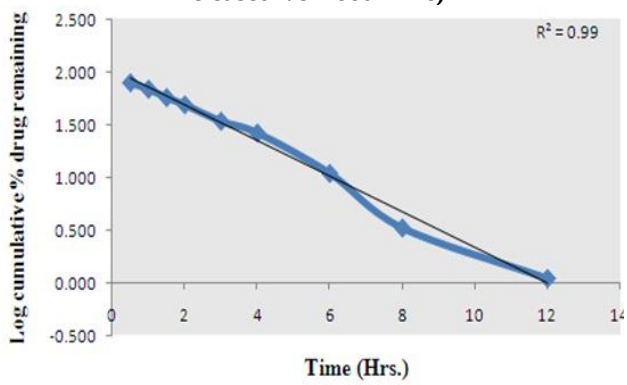
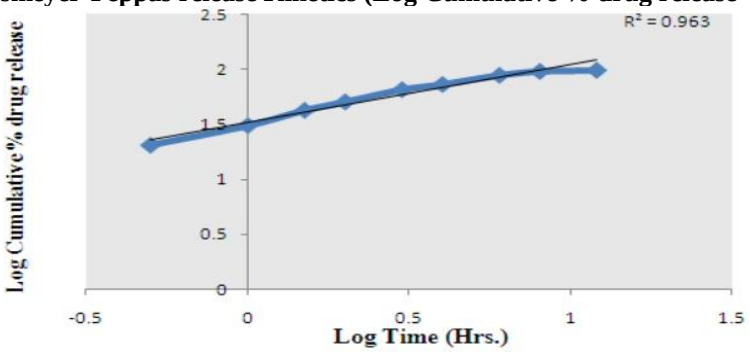


Figure 5 Korsmeyer-Peppas release Kinetics (Log Cumulative % drug release Vs Log Time)



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DISCUSSION

Floating gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

The preliminary study showed that Gemfibrozil is White to off-white and Odorless powder. It is freely soluble in methanol soluble in ethanol and 0.1 N Hydrochloric acids, slightly soluble in 0.1 N NaOH, The melting point was in the range of 58-61°C which is compliance with the standard value.

Identification of Gemfibrozil was performed by UV/VIS Spectroscopy. The 10 µg/ml solutions of Gemfibrozil was scanned in the range of 200-400nm to determine the λmax for drug. The λ_{max} of Gemfibrozil was found to be 278nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25 µg/ml Gemfibrozil was prepared and scanned in UV region. Their absorbances were noted at 278.0 nm and calibration curve was plotted as absorbance *vs* concentration and their linearity range was determined.

From the FT-IR data of the physical mixture obviously functionalities of drug have stayed unaltered including forces of the peak. Preformulation studies reported that the formulation of floating of Gemfibrozil can be prepared with appropriate methods.

Floating gastro retentive tablets containing Gemfibrozil were prepared using direct compression method. Total nine formulations were prepared using varying amount of HPMC-K4 and HPMC-K15. The prepared Tablets were further evaluated for Hardness, Friability, floating behavior, and uniformity of drug content, and In-vitro Release Studies.

Percentage assay of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 95.58±0.54 - 98.96±0.65%.

The maximum percentage buoyancy and floating lag time was found to be formulation F7 in gastro retentive tablets. The optimized formulation of batches subjected to further studies.

The *In vitro* drug release information of the enhanced detailing was subjected to integrity of fit test by linear regression analysis as indicated by zero order, first order kinetic equation, in order to decide the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of First order was maximum *i.e.* 0.990 hence indicating drug release from formulations was found to follow First order Hixson-Crowell release kinetics.

CONCLUSION

Gemfibrozil is used along with a proper diet to help lower fats (triglycerides) and raise "good" cholesterol (HDL) in the blood. It may also help to lower "bad" cholesterol (LDL). Gemfibrozil belongs to a group of drugs known as "fibrates." It works by decreasing the amount of fat produced by the liver. Lowering triglycerides in people with very high triglyceride blood levels may also decrease the risk of pancreas disease (pancreatitis).

The floating tablets of Gemfibrozil were successfully prepared by direct compression method and confirmed that it is a best method for preparing Gemfibrozil tablets. The formulation F-7 of gastroretive tablets showed better release rate compare to other formulations. The in vitro dissolution studies showed that Gemfibrozil tablets formulation F7 showed better sustained effect over a period of 12 hours than floating formulations.

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