Available online on 23.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation, Development and Evaluation of Bilayer Floating Tablet of Gemfibrozil

Mohammad Faizan Mohammad Gufran*[1], Sailesh Kumar Ghatuary[1], Reena Shende[1], Prabhat Kumar Jain[2], Geeta Parkhe[2]

[1] RKDF School of Pharmaceutical Science, Bhopal (M.P.), India

[2] Scan Research Laboratories, Bhopal (M.P.), India

ABSTRACT

Formulation development is an important part of drug design and development. Bioavailability and bioequivalence are totally dependent on formulation development. Now-a-days formulation development is done by following QbD (Quality by Design).The aim of present study is to formulate Gemfibrozil (Gem) sustained release (SR) and immediate release (IR) bilayer tablet by different concentration of Hydroxypropyl methylcellulose (HPMC) and HPMC K 100 M to control the release pattern. The sustained release layer of Gem was prepared by using different grades of HPMC like, HPMC K-15, HPMC K-4 along with other excipients by direct compression technique. The immediate release layer of Gem was prepared by Cross carmellose sodium, Crospovidone and Sodium starch glycolate by direct compression technique. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The both immediate release and sustained release layers of Gem were characterized by FT-IR and in vitro dissolution studies. The drug release study of Gem was evaluated using USP-II paddle type dissolution apparatus. The release rate of Gem in immediate release layer was studied for 15 min in 0.1 N HCL media and that of Gem in sustained release layer was studied for 12 h in 0.1 N HCL. From the nine batches F6 batch showed good release behaviour 99.85% of drug is released over 12 hours. Gem belongs to BCS Class II (log P 3.6) with poor solubility and high permeability resulting in limited and variable bioavailability. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guideline.

Keywords: Bilayer floating tablets, Gemfibrozil, Biphasic drug release, HPMC K 15.

Article Info: Received 22 June 2019; Review Completed 31 July 2019; Accepted 18 August 2019; Available online 23 August 2019

Cite this article as:

Mohammad Gufran MF, Ghatuary SK, Shende R, Jain PK, Parkhe G, Formulation, Development and Evaluation of Bilayer Floating Tablet of Gemfibrozil, Journal of Drug Delivery and Therapeutics. 2019; 9(4):574-578

http://dx.doi.org/10.22270/jddt.v9i4.3401

***Address for Correspondence:**

Mohammad Faizan Mohammad Gufran, RKDF School of Pharmaceutical Science, Bhopal (M.P.)

INTRODUCTION

The bilayer tablet is a concept which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs[1]. Floating Bilayer drug delivery system is combined principle of bilayer tablet as well as floating mechanism. Floating Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose[2]. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[3]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate[4,5]. Gemfibrozil (Gem) is a widely used antihyperlipidemic agent classified as fibric acid derivative. It increases the activity of extrahepatic lipoprotein lipase, resulting in the lipolysis process[6]. Gem activates peroxisome proliferator-activated receptor-alpha transcriptor factor ligand, a receptor that is involved in the metabolism of carbohydrates and fats and also in adipose tissue distribution[7]. This results in increased synthesis of lipoprotein lipase thereby increasing the clearance of triglyceride. Gem belongs to BCS Class II (log P 3.6) with poor solubility and high permeability resulting in limited and variable bioavailability[8,9]. In the present study, a bilayer tablet for bimodal drug release in which one layer of immediate release and second layer of sustained release of Gem was designed by direct compression method.

MATERIALS AND METHODS

Gem was obtained from Aurobindo Pharma, Hyderabad, as a gift sample. HPMC K4, K15, PVP K30 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Procedure for the determination of λ_{max}

Accurately weighed 10 mg of Gem separately and dissolved in 10 ml of 0.1N HCL in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 100 µg/ml make adequate of sample with concentration range of 5-25µg/ml Gem calculate the spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (Labindia UV 3000 +). The higher absorption peak was obtained at 278nm which was the λmax of drug.

Formulation development

Formulation of immediate release (IR) layer

The immediate release granules were prepared by blending the drug with different concentration of superdisintegrants like sodium starch glycolate, crospovidone, croscarmellose sodium and other excipients like microcrystalline cellulose by direct compression method. The powder blend was lubricated with magnesium stearate and talc. A weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 16 station Rimek mini press rotary compression machine to get IR layer. Nine formulation batches with different super superdisintegrants were made in order to achieve desired disintegration time and drug release. The composition of Gem immediate release tablets were shown in Table 1.

Formulation of floating sustained release (SR) layer

The floating sustained release granules were prepared by direct compression technique. Required quantity of Gem and polymers like HPMC K4, HPMC K15, PVP K30, alkalizing agent sodium bicarbonate and acidifying agent citric acid were weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 min and was taken in a mort. The powder mass was passed through mesh #14. Finally the powder was lubricated with lactose and talc Table 2.

Formulation of bilayer tablet

Optimized formulation IF-6 of immediate release layer and optimized formulation of F-6 for sustained release used for formulation of Bi-layer tablet.

Table 1 Composition of Gemfibrozil fast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Gemfibrozil	200	200	200	200	200	200	200	200	200
Sodium Starch glycolate	15	20	25	-	-	-	-	-	-
Croscarmellose sodium		-	-	15	20	25	-	-	-
Crospovidone		-	-	-	-	-	15	20	25
Microcrystalline cellulose	24	19	14	24	19	14	24	19	14
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	250	250	250	250	250	250	250	250	250

Table 2 Formulation of sustained release floating layer

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gemfibrozil	400	400	400	400	400	400	400	400	400
HPMC K 15	- -	- -	--	100	120	140	50	60	70
HPMC K 4	100	120	140	--	--	--	50	60	70
PVP K30	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	15	15	15	15	15	15	15	15	15
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	60	40	20	60	40	20	60	40	20
Total Weight	600	600	600	600	600	600	600	600	600

Evaluation of precompression parameter

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula[10-12].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

General appearance

Morphological characters like shape and texture was determined visually.

Thickness

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) and measured in terms of kg/cm^2.

Weight variation

The weight variation test was performed as per the U.S guidelines. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCL and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ max of 278.0nm using of 0.1 N HCL as blank.

Buoyancy lag time determination & total floating time

In vitro buoyancy was determined by floating lag time as per the method described below. The tablets were placed separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation.

In vitro disintegration time of immediate release tablets

The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted.

In vitro dissolution studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5^{0}C and rpm of 75. One Betahistine tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^{0}C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 278nm using spectroscopy.

Stability studies

The stability of Gem bilayer floating tablets to assess their stability with respect to their physical appearance, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properly closed HDPE bottles along with 1 g desiccant for 3 months.

RESULTS AND DISCUSSIONS

Solubility of Gem was soluble in ethanol, methanol, chloroform, 0.1N HCl water, sparingly soluble in water, 0.1 N NaOH, 6.8 pH Phosphate buffer. The melting point of Gem was 58-61°C and λ_{max} of Gem was found to be 278 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml Fig.1.

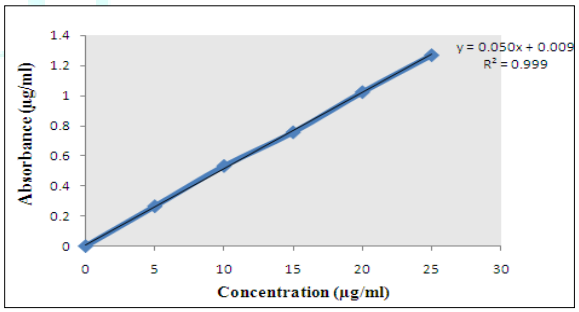

Fig. 1Calibration curve of gemfibrozil in 0.1 HCL at 278 nm

The powdered blends of different formulations of immediate release tablets and sustained release floating tablets were evaluated for angle of repose, bulk density (BD), tapped density (TBD) and compressibility index. The results of immediate release tablets and SR floating tablets are summarized in Table 3& 4. The results of SR floating tablets of BD and TBD ranged from 0.478to 0.489and 0.571to 0.589respectively. The range of Hausner ratio and compressibility index was found to be 1.168 to 1.230 and 14.361to 18.676respectively. The results of angle of repose (<25) indicate good flow properties of the powdered blend. The formulation of immediate release tablet prepared by

using the superdisintegrants exhibited the LBD, TBD, angle of repose, compressibility index and Hausner's ratio of within the range, which shows good flow properties of the powdered blend.

Table 3 Results of pre-compression parameters of powder blend of immediate release

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.456	0.535	14.766	1.173
IF2	0.469	0.536	12.500	1.143
IF3	0.476	0.537	11.359	1.128
IF4	0.471	0.532	11.466	1.130
IF5	0.475	0.541	12.200	1.139
IF6	0.479	0.539	11.132	1.125
IF7	0.475	0.541	12.200	1.139
IF8	0.472	0.532	11.278	1.127
IF9	0.476	0.541	12.015	1.137

Table 4 Result of pre-compression properties of sustained release floating tablets

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner's ratio
F1	0.489	0.578	15.398	1.182
F2	0.485	0.582	16.667	1.200
F3	0.482	0.579	16.753	1.201
F4	0.479	0.589	18.676	1.230
F5	0.485	0.578	16.090	1.192
F6	0.489	0.571	14.361	1.168
F7	0.482	0.573	15.881	1.189
F8	0.485	0.574	15.505	1.184
F9	0.478	0.582	17.869	1.218

The prepared tablets were evaluated for different physico-chemical properties and the results are summarized in Table 5 & 6. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friability and content uniformity of different batch of tablets were found within acceptable range and the distribution of drug in all the formulations was uniform.

Table 5 Results of post-compression parameters of immediate release

F. Code	Hardness test (kg/cm²)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (sec.) (n=3) Mean ± SD
IF1	3.2	0.856	255	2.45	95.56	115±8
IF2	3.4	0.789	250	2.42	97.89	98±9
IF3	3.3	0.658	256	2.39	98.85	88±8
IF4	3.4	0.456	260	2.45	98.78	125±9
IF5	3.4	0.521	245	2.48	98.85	110±6
IF6	3.5	0.478	248	2.43	99.25	105±8
IF7	3.4	0.652	252	2.42	98.78	165±9
IF8	3.4	0.745	255	2.41	97.78	133±9
IF9	3.4	0.658	255	2.43	98.85	120±5

Table 6 Results of post compression properties of sustained release floating tablets

F. Code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating lag times (sec)	Total Floating Time (hrs)
F1	3.45	5.2	605	0.658	98.78	56	>12
F2	3.52	5.3	610	0.554	98.12	58	>12
F3	3.49	5.4	595	0.587	99.12	62	>12
F4	3.41	5.2	588	0.478	97.85	78	>12
F5	3.51	5.2	596	0.489	98.65	85	>12
F6	3.48	5.3	605	0.458	99.25	92	>12
F7	3.47	5.4	610	0.569	99.32	85	>12
F8	3.49	5.2	605	0.854	99.56	94	>12
F9	3.47	5.1	595	0.658	98.98	81	>12

The prepared bilayer tablets were evaluated for different physico-chemical properties and the results are summarized in Table 7. The tablets were found to be uniform with respect to weight variation and hardness (6.20±0.2kg/cm²). The thickness (5.42±0.03mm) and friability (0.658±0.062%) of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 98.96%, where the distribution of drug in all the formulations was uniform.

Table 7 Post-compressional parameters of bilayer tablets

Formulation	Hardness test (kg/cm²)	Friability (%)	Weight variation	Thickness (mm)	Gemfibrozil (% Label Claim)
1.	6.20±0.2	0.658±0.062	Passes	5.42±0.03	98.96

The Instant layer of Gem release Approx 98.00±1.23 percent drug within 15 minutes and control floating layer Gem shows release up to 12 Hours Approx 99.89 percent. The release of bilayer tablet is shown in Fig.2.

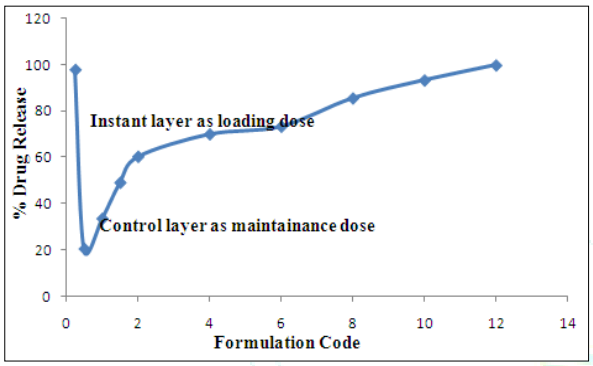

Fig. 2 Graph of release of bilayer tablets

CONCLUSION

Based on the above study, it can be concluded that Gemfibrozil, a conventional drug for antihyperlipidemic activity can be successfully formulated in the form of bilayer tablet by optimizing drug polymer ratio using different grades of common polymers like HPMC K4, HPMC K 15 etc. This is basically done to improve bioavailability of the drug and better therapeutic compliance. The sustained layer of the drug showed steady state release behaviour over a prolonged duration of time which may reduce dose related side effects. In future, natural biodegradable polymers can be used to improve therapeutic efficacy of the drug and further minimizing side effects.

ACKNOWLEDGMENTS

The authors would like to thank the Mr. Prabhat Kumar Jain, Geeta Parkhe and All supporting staff of Scan Research Laboratories, Bhopal (M.P.) who helped in the experiments during research work.

REFERENCES

1. Shaikh TK, Gadhave MV, Jadhav SL, Gaikwad DD. Different techniques of bilayer tablet: a review. Int J Univ Pharm Life Sci 2012; 2(2): 450-460.
2. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A review. J Pharm Tech 2008; 1(14): 345-348.
3. Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, Acta Pharm 2007; 57: 479-489.
4. Deshpande RD, Gowda DV, Mahammed M, Maramwar DN, Bi-Layer tablets-an emerging trend: a review, Int J Pharm Sci Res2011; 2(10); 2534-2544.
5. Yadav BV, Yadav VA. Enhancement of solubility and dissolution rate of BCS class II pharmaceuticals by nonaquious granulation technique. Int J Pharma Res Devel 2010; 1: 1-12.
6. Taneja S, Shilpi S, Khatri K. Formulation and optimization of efavirenz nanosuspensions using the precipitation-ultrasonication technique for solubility enhancement. Artif Cells Nanomed Biotechnol 2016; 44:978-84.
7. Patel R, Baviskar T, Rajput A. Development and in-vivo characterization of SMEDDs (self-microemulsifying drug delivery system) for gemfibrozil. Int J Pharm Pharm Sci 2013; 5:793-800.
8. Talib H, Watersa L, Gareth M, Parkes G. Microwave processed solid dispersions for enhanced dissolution ofgemfibrozil using non-ordered mesoporous silica. Colloids Surf A Physicochem Eng Asp 2017;520:428-35
9. Huang QP, Wang JX, Chen GZ, Shen ZG, Chen JF, Yun J. Micronization of gemfibrozil by reactive precipitation process. Int J Pharm 2008; 360:58-64.
10. Liberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablets, 3rd edition, Marcel Dekker, New York, 1990.
11. Lordi GN. Sustained release dosage forms. In: Lachman L, Liberman HA, Kanig JL, 3rd edition. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House; 1987:430-456;
12. Aulton ME; Wells TI; Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, London, England, 1988.