FORMULATION AND EVALUATION OF FLOATING *IN-SITU* GEL OF FENOFIBRATE

Pinky Gupta[1]*, Kamal Singh Rathore[2]

Abstract

Objective: In the present research work, the aim was to prepare ion induced *in-situ* floating gel of fenofibrate to improve oral bioavailability.

Methods: *In-situ ion* induced floating gel was prepared by with ion induced gelling agent, a one viscosity builder polymer and calcium carbonate. The amounts of polymers were selected on the basis of optimum quantity required for sustained release of drug from preparation and as reported in literature and performed ranging study.

Results and discussion: Sodium alginate and Calcium Carbonate were used to prepare ion induced *in-situ* floating gel. All formulation was evaluated for Appearance, pH, viscosity, *In-vitro* buoyancy test, gelling capacity, % drug content and release study. Nine formulations were prepared and optimized successfully using 3^2 factorial designs. Optimization was done by DoE software version Version 12.0.10.064.

Conclusion: Fenofibrate was successfully formulated into ion induced *in-situ* floating gelling system using Sodium alginate in combination with Calcium carbonate. It was seen that Sodium alginate is important for *in-situ* gel behaviour along with Calcium carbonate on the basis of main effect of concentration of Sodium alginate and Calcium carbonate. *In-vitro* results indicated that the *in-situ* floating gel system is a viable alternative to conventional oral dosage form by virtue of its ability to sustain drug release.

Keywords: Sodium alginate, guar gum, calcium carbonate, ion induced *in-situ* floating gel, and bioavailability.

[1*,2]BN. College of Pharmacy, B.N. University, Rajasthan, India. [1]*Email:pinkyguptapharma@gmail.com

***Corresponding author:** Pinky Gupta
*BN. College of Pharmacy, B.N. University, Rajasthan, India. [1]*Email:pinkyguptapharma@gmail.com

DOI: 10.53555/ecb/2022.11.10.213

INTRODUCTION

Fenofibrate (FBT) is a lipophilic drug which is used in treatment of hypercholesterolemia and hypertriglyceridemia, but the drug have low oral bioavailability. To obtain effective therapy and to improve the therapeutic efficiency of the drug one has to overcome the absorption drawback associated with certain class of drugs by improving its bioavailability. Among the drug delivery systems, gastric oral floating drug delivery systems are desirable especially when the bioavailability of the drugs reduces due to the pathophysiology of the patient. Gastro-retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of the drugs. Prolonged gastric-retention improves bioavailability, reduces drug waste, and improves solubility of drugs which are less soluble in a high pH environment.

The purpose of the present work is to develop an oral *in situ* gel system by using natural polymer i.e., sodium alginate and guar gum along with calcium carbonate for *in-situ* gelation of fenofibrate in order to increase the gastric residence time, the oral bioavailability and for modulate of the release kinetics of the drug. A full 3^2 factorial design is performed to study the effect of variation in concentrations of sodium alginate and calcium carbonate on percentage of drug release.

MATERIALS AND METHODS

Fenofibrate were procured from Indian Pharmaceutical company as a gift sample. Sodium alginate, Calcium carbonate, guar gum. sodium citrate and purified water (In-house) and other chemical and solvents were of analytical grade/IP/BP/USP equivalent grade available in laboratory.

FORMULATION DEVELOPMENT OF FENOFIBRATE FLOATING *IN-SITU* GEL

Preparation of fenofibrate floating *In-Situ* Gel

Sodium alginate (1-1.5% w/v) and sodium citrate (0.5% w/v) were dissolved in Purified water followed by addition of guar gum (0.4% w/v) with stirring for 30 min. Calcium carbonate (0.5-1% w/v) was separately dissolved in purified water. Both solutions were mixed and the drug was added and stirred till it was completely dispersed.

The current study will utilize a complete 3^2 factorial design to investigate impact of two key variables: Sodium alginate (X_1) and Calcium carbonate (X_2), at three different concentration levels. Table 1 displays the variables and their corresponding levels. Nine formulations will be prepared in total, resulting from 3X3 combinations. Table 2 displays composition of formulations using a full factorial design for fenofibrate floating *In-Situ* Gel.

Table 1: Variables and their levels for preparation of fenofibrate floating *In-Situ* Gel

levels / factors	Low (-1)	Medium (0)	High (+1)
Sodium alginate (%) (X1)	1	1.5	2
Calcium carbonate (%) (X2)	0.5	0.75	1

Table 2: Full 3^2 factorial design for the preparation of fenofibrate floating *In-Situ* Gel

Batch Code	P1	P2	P3	P4	P5	P6	P7	P8	P9
Fenofibrate (gm)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sodium alginate (%w/v)(X1)	**1**	**1**	**1**	**1.5**	**1.5**	**1.5**	**2**	**2**	**2**
Calcium carbonate (%w/v)(X^2)	**0.5**	**0.75**	**1**	**0.5**	**0.75**	**1**	**0.5**	**0.75**	**1**
Guar gum (%)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Sodium citrate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Purified water	Q.s.100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml	Q.s. 100 ml

EVALUATION OF THE PREPARED FENOFIBRATE FLOATING *IN-SITU* GEL

Physical examination of the fenofibrate floating *In-Situ* Gel

Fenofibrate floating In-Situ Gel were visually assessed for color and homogeneity.[100]

Measurement of pH of the prepared fenofibrate floating *In-Situ* Gel

pH of fenofibrate floating *In-Situ* Gel was measured utilizing a Lab India digital pH meter. The pH of the *in situ* solution was measured using the standardized digital pH meter at room temperature by taking adequate volume in a 50 ml beaker.

Rheological studies using Brookfield viscometer

Viscosity of fenofibrate floating *In-Situ* gel was measured utilizing a Brookfield viscometer with spindle 62. Formulations were left at a room temperature for 60 minutes for evaluation. The spindle was put vertically into the beaker, ensuring that it did not make contact with the bottom.

Viscosity was tested at 100 revolutions per minute (rpm). Three readings, taken at various places, were averaged. Viscosity of formulations was tested at solution stage.

***In vitro* gelling capacity**

The *in vitro* gelling capacity of the formulations was measured by placing 5 ml of the gelation solution in simulated gastric fluid (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube maintained at 37±1ºC temperature. The formulation (1 ml) was added slowly by placing the pipette at the surface of fluid in the test tube. As the solution comes in contact with gelation solution, it is immediately converted into a stiff gel like structure. The gelling capacity of solution was graded in three categories evaluated on the basis of stiffness of the formed gel and time period for which the gel retained its rigidity.

(+) Gels after five min, dispersed within 8 h

(++) Gels within 60 sec and retains gel structure for 12 h

(+++) Gels immediately and retains gel structure for more than 12 h.

***In-vitro* buoyancy test**

In-vitro buoyancy was characterized by floating lag time and total floating duration. This study was carried out using 0.1N HCl (pH-1.2) as the medium at 37±0.5°C. The *in-situ* gelling solution (10 ml) was transferred to a medium. The time required for the gelled mass to rise to the surface of the dissolution medium [floating lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [floating duration] was noted for each formulation.

Drug content determination of prepared *in-situ* floating gels

For drug content *in situ* solution (equivalent to 100 mg of fenofibrate) was taken in a volumetric flask. To this 100 ml of methanol was added and shaken on the mechanical shaker for 30 min. This was followed by sonication for 15 min for complete dispersion of contents and filtration using 0.2 µm nylon syringe filters. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with methanol and another 1 ml from diluted solution taken in 10 ml flask and diluted to 10 ml with nmethanol. Contents of fenofibrate were determined spectro-photometrically at 283.5 nm using double beam UV-visible spectrophotometer.

***In-vitro* drug release**

The drug release study was carried out using USP type II paddle type apparatus at 37±0.5ºC and at 50 rpm using 900 ml of 0.75% w/v of SLS solution. *In-situ* gel (10 ml) equivalent to 100 mg of fenofibrate was used for the test. Sample solution (5 ml) was withdrawn at predetermined time intervals, filtered through a 0.2 µm nylon syringe filters, diluted suitably and analyzed by UV spectrophotometric at 290 nm. Fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain sink condition. The dissolution studies were carried out for a period of 6 h.

RESULTS AND DISCUSSION

Preparation of Fenofibrate Floating *In-Situ* Gel

Figure 1 displays an image of the completed formulation.

(a)

(b)

Figure 1: (a) Fenofibrate floating *In-Situ* Gel in solution stage (b) Picture of floating gel

EVALUATION OF THE PREPARED FENOFIBRATE FLOATING *IN-SITU* GEL

Physical examination of the fenofibrate floating *in-situ* Gel

The prepared physical examination of the fenofibrate floating *in-situ* gels were evaluated for their physical appearance and it was found that prepared formulations were white to of white, viscus, as well as homogenous. The findings are displayed in Table 3.

Table 3: Physical examination of the prepared fenofibrate floating *In-Situ* Gel

Formulation	Colour	Homogeneity
P1	White to of white, viscus	Homogenous
P2		
P3		
P4		
P5		
P6		
P7		
P8		
P9		

Measurement of pH of the prepared fenofibrate floating *In-Situ* Gel

The pH was observed in the acceptable range of 7-8. The findings are displayed in Table 4.

Table 4: pH of prepared floating *in-situ* gel formulations of fenofibrate

Formulation	pH*
P1	7.2±0.1
P2	7.2±0.3
P3	7.2±0.2
P4	7.3±0.3
P5	7.5±0.1
P6	7.7±0.2
P7	7.4±0.4
P8	7.5±0.1
P9	7.6±0.3

*Data indicate mean ± std. deviation of triplicate determinations

Rheological studies using Brookfield viscometer

The solution showed a marked increase in viscosity with increasing concentration of sodium alginate and calcium carbonate and due to the presence of guar gum. The calcium carbonate content in the formulation simultaneously increased the viscosity since it was present in the formulation as insoluble dispersion, an increasing concentration of polymer thus contributing to

increased viscosity. The order of viscosity of all formulations were P9 > P8 > P7 > P6 > P5 > P4 > P3 > P2 > P1. It was found to be in the range of 185.2-368.3 cps.

Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30s shown in Table 5.

Table 5: Viscosity of prepared floating *in-situ* gel formulations of fenofibrate

Formulation	Viscosity* (cps)
P1	186.2±0.75
P2	198.9±0.85
P3	205.4±0.29
P4	258.4±0.53
P5	270.0±0.15
P6	288.3±0.12
P7	322.4±0.27
P8	346.01±0.31
P9	368.3±0.30

*Data indicate mean ± std. deviation of triplicate determinations

Average effect of varied concentrations of sodium alginate and calcium carbonate on the viscosity of the prepared floating *in-situ* gel formulations of fenofibrate at solution stage is presented in Table 6.

Table 6: Average effect of varied concentrations of sodium alginate and calcium carbonate on viscosity at solution stage

Name of Polymer	Polymer's Concentration	Formula for Calculating Average effect	Values as per formula	Average effect (cps)
Sodium alginate	1.00	(P1+P2+P3)/3	(186.2+198.9+ 205.4)/3	196.83
	1.50	(P4+P5+P6)/3	(258.4+270.0 + 288.3)/3	272.23
	2.00	(P7+P8+P9)/3	(322.4+346.01+ 368.3)/3	345.57
Calcium Carbonate	0.50	(P1+P4+P7)/3	(186.2+258.4+ 322.4)/3	255.66
	0.75	(P2+P5+P8)/3	(198.9+270.0 +346.01)/3	271.63
	1.00	(P3+P6+P9)/3	(205.4+288.3+ 368.3)/3	287.33

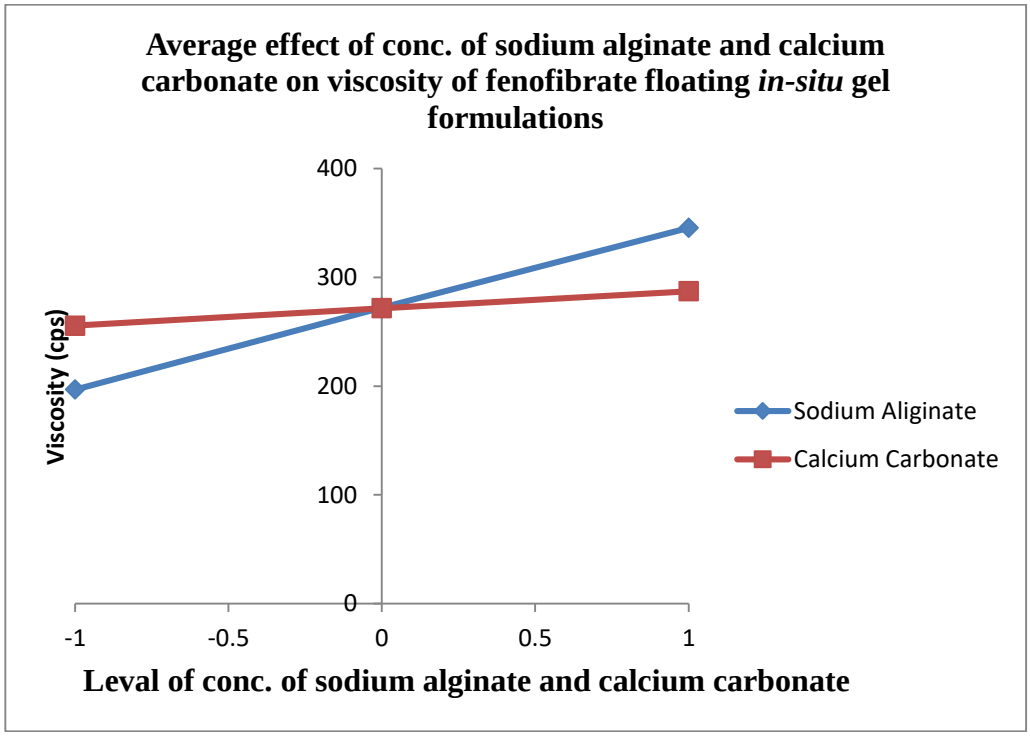

Figure 2: Average effect of conc. of sodium alginate and calcium carbonate on viscosity of fenofibrate floating *in-situ* gel formulations

Data was analysed by ANOVA and it was found that increase in conc. of sodium alginate from 1% to 2% resulted in significant ($P<0.05$; df= 2,6; $F_{crit}=5.14$; $F=58.59$) increase in viscosity. However, increase in conc. of calcium carbonate from 0.5% to 1% resulted in insignificant ($P<0.05$; df= 2,6; $F_{crit}=5.14$, $F=0.13$) increase in viscosity.

Main and interaction effects of independent variables on viscosity are shown in Figure 3 and 4 respectively.

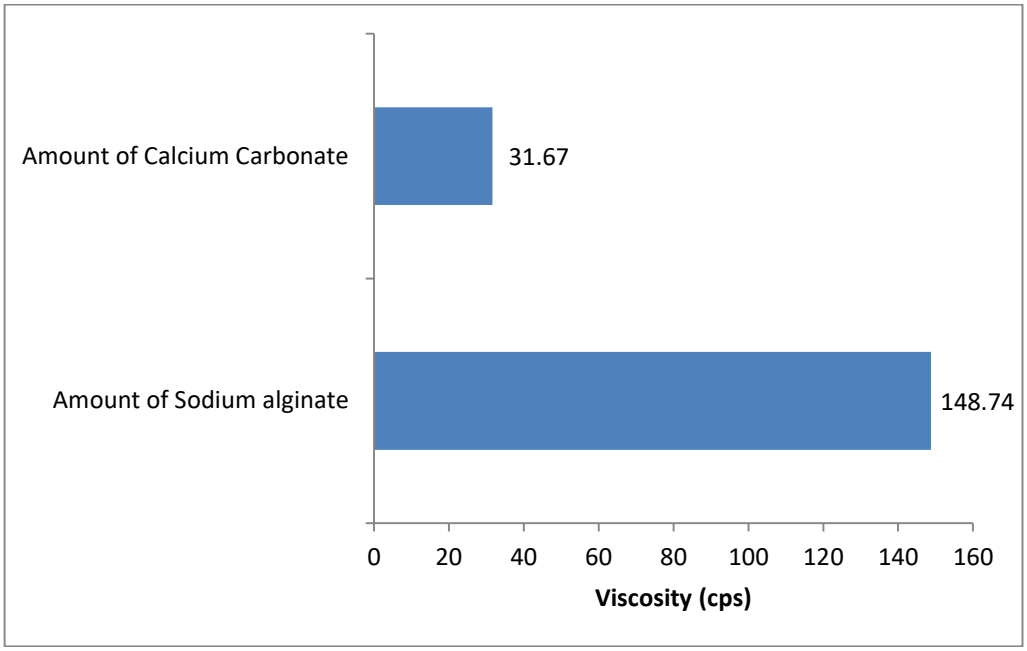

Figure 3: Main effect of conc. of sodium alginate and calcium carbonate on viscosity of fenofibrate floating *in-situ* gel formulations

Based on the main effect as shown in figure 3, out of the two parameters, conc. of sodium alginate influences viscosity to a greater extent.

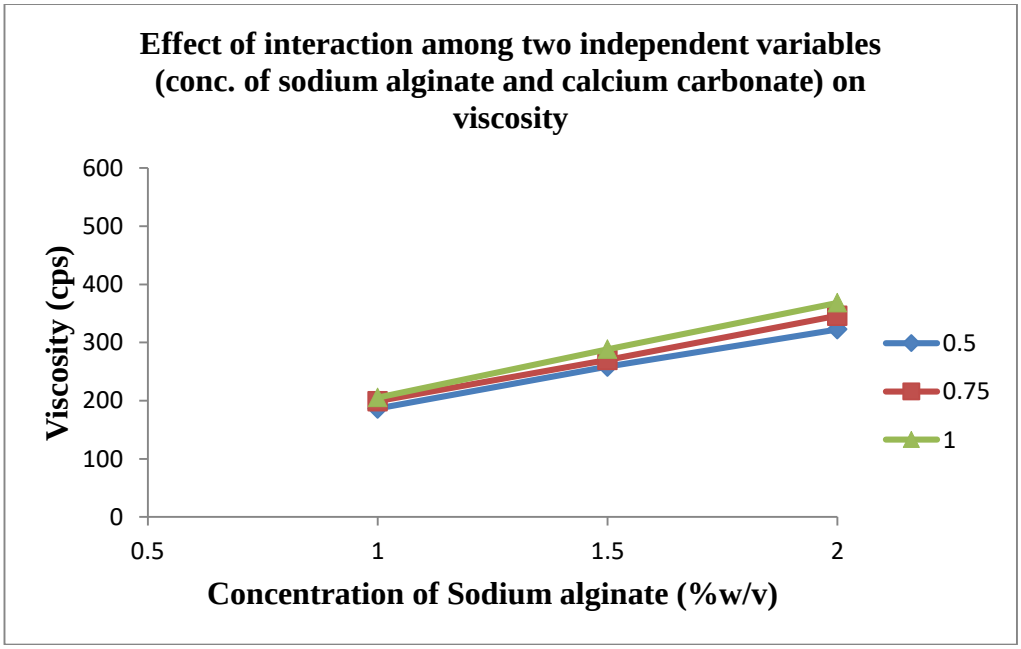

Figure 4: Effect of interaction among two independent variables (conc. of sodium alginate and calcium carbonate) on viscosity of fenofibrate floating *in-situ* gel formulations

Figure 4 shows a two dimensional plot showing the effect of interaction among the two variables (conc. of sodium alginate and calcium carbonate) on viscosity of the floating *in-situ* gel of fenofibrate. The relative slopes of lines within plot indicate if interaction is present. Reach of

parallelism of lines in figure 4 indicates interaction between concentration of sodium alginate and calcium carbonate.

In vitro gelling capacity

The pre-requisites for *in-situ* gelling system is gelling capacity which is defined in terms of speed and extent of gelation. The *in-situ* gel should maintain its integrity without dissolving or eroding for prolonged periods to facilitate controlled release of drugs locally. From the results, it was observed that (P1-P4) batches form gel within 60 sec and retains gel structure for 12 h whereas (P5-P9) batches, which contains high amount of polymer, form gel within few seconds and remained in their gel state for more than 12 h without losing their integrity.

Table 7: *In-vitro* gelling capacity of prepared floating *in-situ* gel formulations

Formulation	*In-vitro* gelling capacity
P1	++
P2	++
P3	++
P4	++
P5	+++
P6	+++
P7	+++
P8	+++
P9	+++

In-vitro buoyancy test

The time required for the gelled mass to rise to the surface of the dissolution medium [floating lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [floating duration] was noted for each formulation and presented in Table 8. The floating and gelling behaviour of *in-situ* gel formulation are shown in Figure 5.

Figure 5: Photograph of floating and gelling behaviour of *in-situ* gel

Table 8: *In-vitro* buoyancy characteristics of prepared floating *in-situ* gel formulations of fenofibrate

Formulation	Floating lag time* (sec)	Duration of floating (h)
P1	18±1.1	12
P2	16±1.3	12
P3	13±1.6	12
P4	15±1.8	12
P5	13±1.5	>12
P6	11±1.2	>12
P7	11±1.9	>12
P8	9±2.1	>12
P9	8±1.0	>12

*Data indicate mean ± std. deviation of triplicate determinations

The floating properties of the formulation mainly depend on calcium carbonate, on increasing the calcium carbonate concentration, the floating lag time was reduced and the duration of floating was extended. The increasing amounts of Ca^{+2} and CO_2 resulted from the increase in calcium carbonate concentration, are responsible for the observed reduction in floating lag time and increasing duration of floating. The floating lag time is minimum for P3 and highest for P1. This is because P3 contains highest concentration of calcium carbonate. Similar was the case with formulation P6 & P4 and P9 & P7. Increase in polymer concentration results in an increase in viscosity. Hence time taken by the sol to form a cohesive gel mass and to emerge on the surface of the medium was lowered.

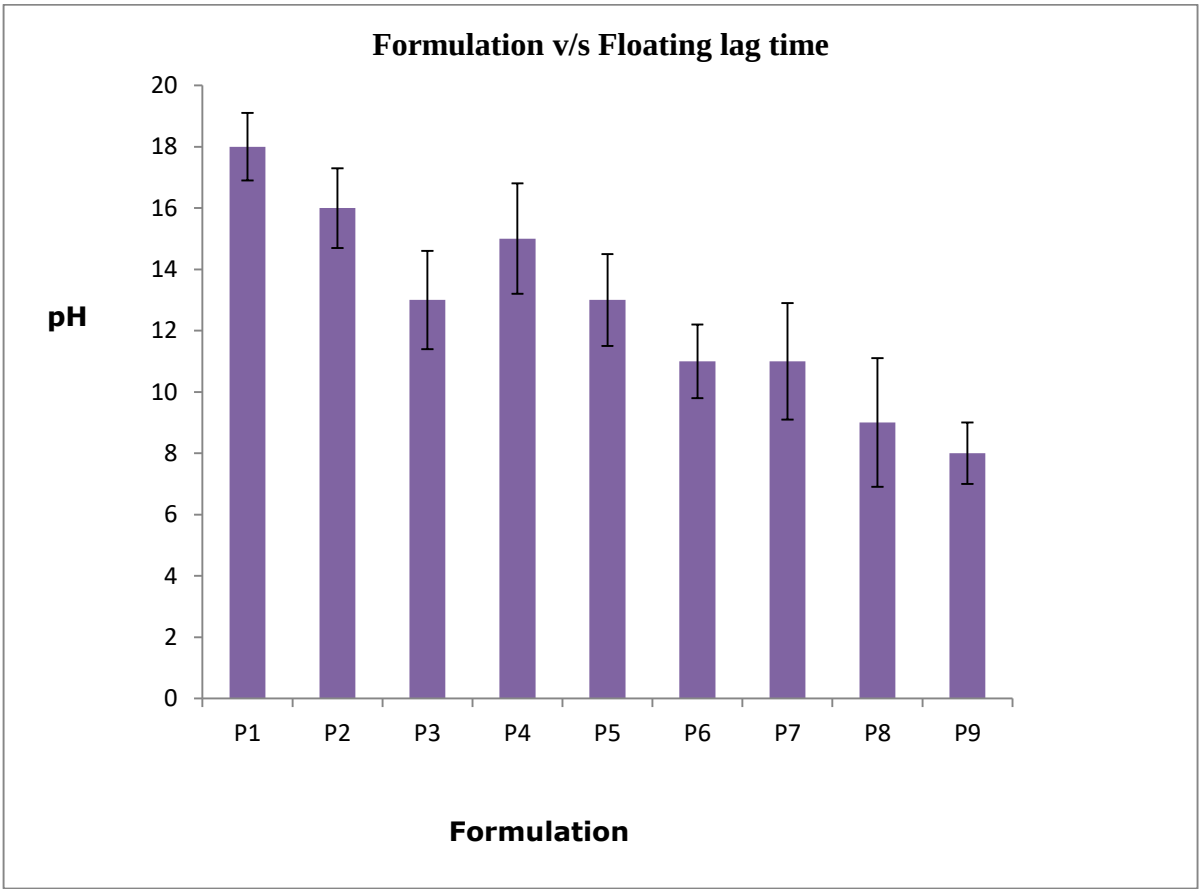

Figure 6: Floating lag time of *in-situ* floating gel of fenofibrate

Average effect of conc. of sodium alginate and calcium carbonate on floating lag time of fenofibrate floating *in-situ* gel formulations of fenofibrate is presented in Table 9 along with Figure 7.

Table 9: Average effect of conc. of sodium alginate and calcium carbonate on floating lag time of fenofibrate floating *in-situ* gel formulations

Name of Polymer	Polymer's Concentration	Formula for Calculating Average effect	Values as per formula	floating lag time (sec)
Sodium alginate	1.00	(P1+P2+P3)/3	(18+16+13)/3	15.66
	1.50	(P4+P5+P6)/3	(15+13+11)/3	13.00
	2.00	(P7+P8+P9)/3	(11+9+8)/3	9.33
Calcium Carbonate	0.50	(P1+P4+P7)/3	(18+15+11)/3	14.66
	0.75	(P2+P5+P8)/3	(16+13+9)/3	8.37
	1.00	(P3+P6+P9)/3	(13+11+ 8)/3	10.66

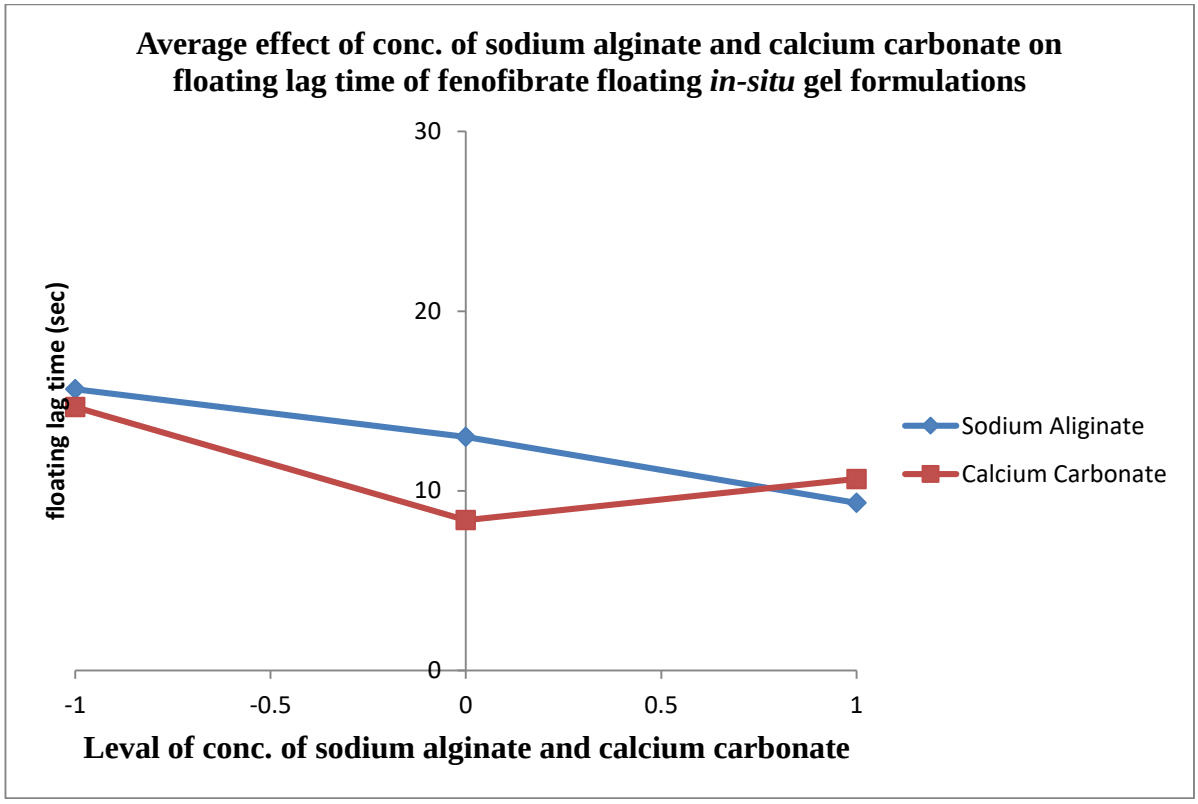

Figure 7: Average effect of conc. of sodium alginate and calcium carbonate on floating lag time of fenofibrate floating *in-situ* gel formulations

Data was analysed by ANOVA and it was found that increase in conc. of sodium alginate from 1% to 2% resulted in insignificant ($P<0.05$; df= 2,6; $F_{crit}=5.14$; $F=1.16$) decrease in FLT. However, increase in conc. of calcium carbonate from 0.5% to 1% resulted in significant ($P<0.05$; df= 2,6; $F_{crit}=5.14$, $F=7.18$) decrease in FLT.

Main and interaction effects of independent variables on floating lag time are shown in Figure 8 and 9 respectively.

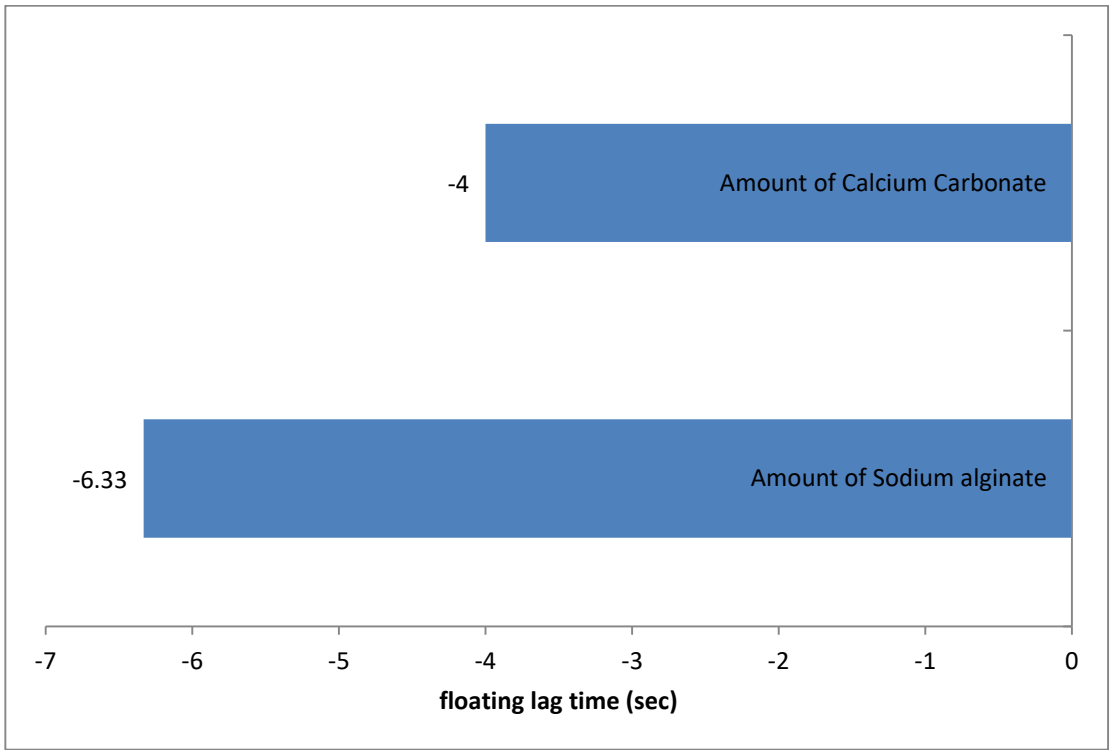

Figure 8: Main effect of conc. of sodium alginate and calcium carbonate on floating lag time of fenofibrate floating *in-situ* gel formulations

Based on the main effect as shown in figure 8, out of the two parameters, conc. of calcium carbonate influences floating lag time to a greater extent.

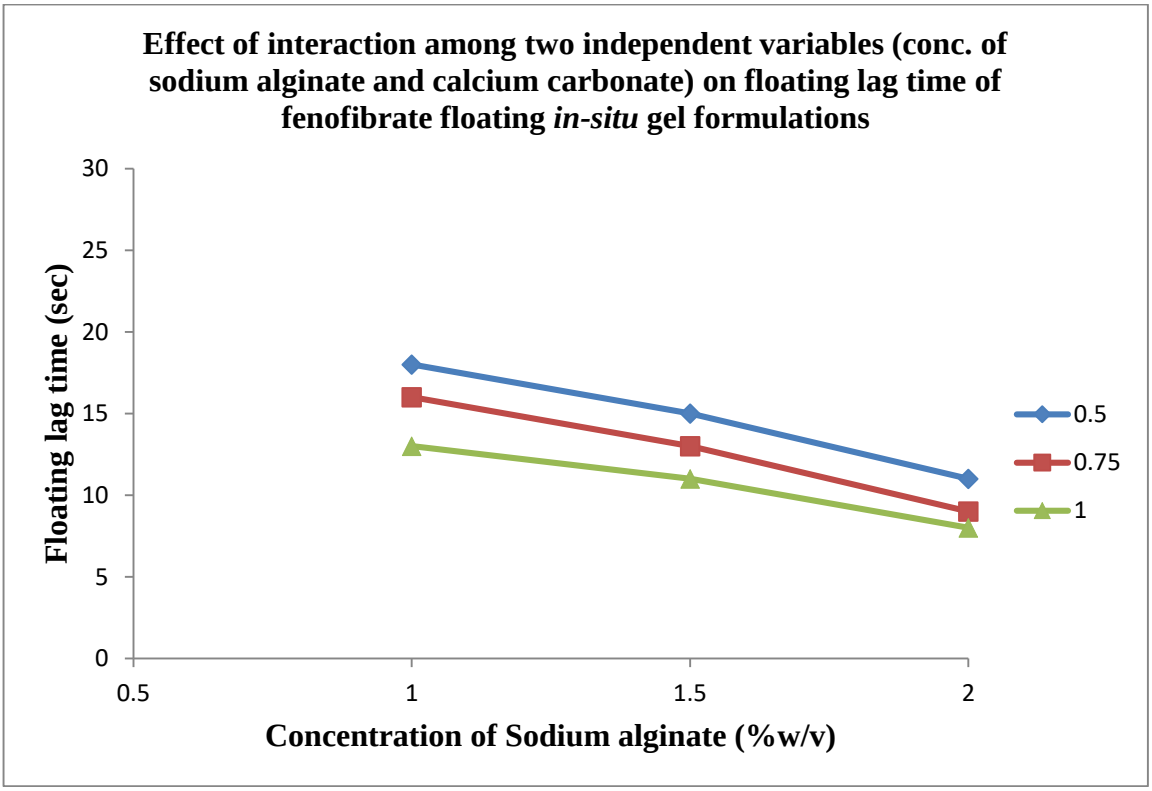

Figure 9: Effect of interaction among two independent variables (conc. of sodium alginate and calcium carbonate) on floating lag time of fenofibrate floating *in-situ* gel formulations

Figure 9 shows a two dimensional plot showing the effect of interaction among the two variables (conc. of sodium alginate and calcium carbonate) on floating lag time of the floating *in-situ* gel of fenofibrate. The relative slopes of lines within plot indicate if interaction is present. Parallelism of lines in figure 9 indicates interaction between concentration of sodium alginate and calcium carbonate.

Drug content determination of prepared *in-situ* floating gels

Drug content for the prepared formulations was observed with high drug loading which is more than 90% showing maximum drug content. The drug content was found to be in the range of 98-102%. The estimated drug content of prepared *in-situ* gel formulations of fenofibrate is presented in Table 10.

Table 10: Drug content of prepared *in-situ* gel formulations of fenofibrate

Formulation	Drug Content* (%)
P1	99.19±1.48
P2	98.16±1.34
P3	98.94±1.44
P4	98.83±1.30
P5	99.52±1.5
P6	99.83±1.23
P7	99.58±1.00
P8	101.27±0.41
P9	100.66±1.02

*Data indicate mean ± std. deviation of triplicate determinations

6.3.7 *In-vitro* drug release

% Drug release results are displayed in Table 10.

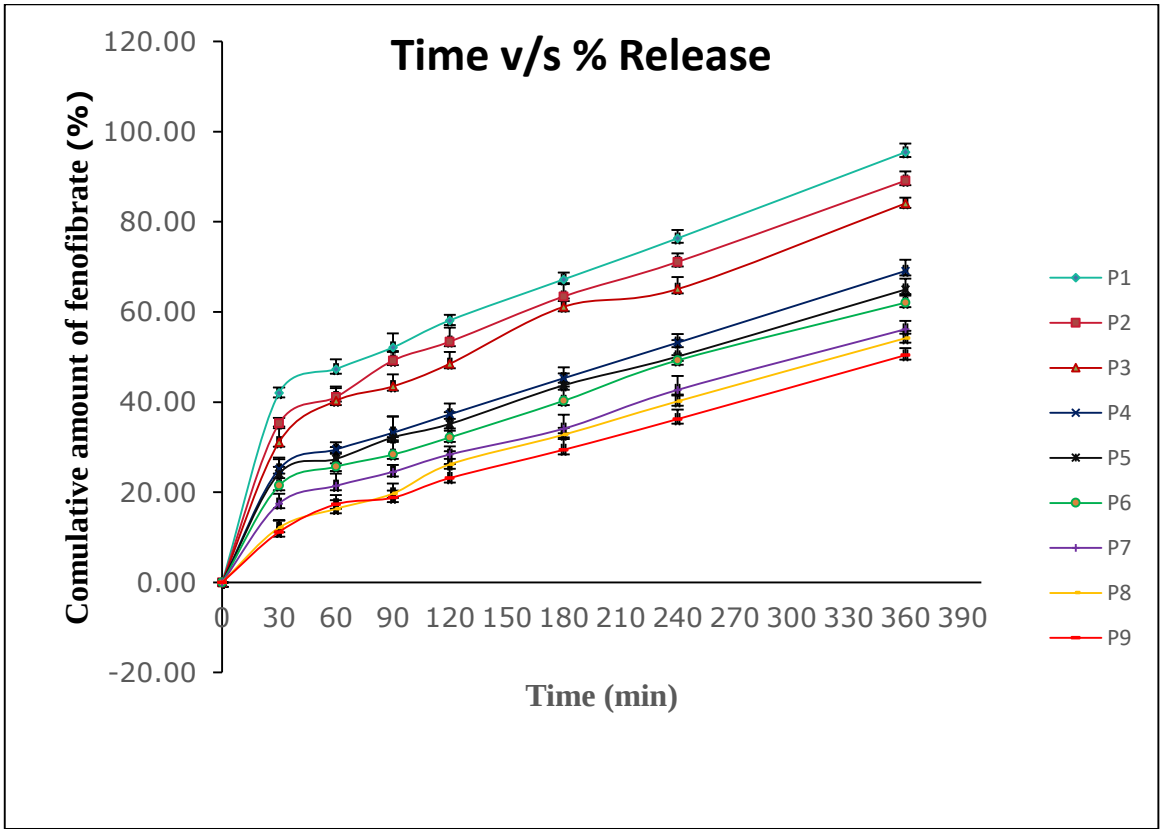

Figure 10: *In-vitro* release of fenofibrate from different formulations

The effect of polymer concentration on *in-vitro* drug release from in situ gels is depicted in (figure 10). A significant decrease in rate and extent of drug release was observed with the increase in polymer concentration, and is attributed to increase in the density of the polymer matrix and also increase in the diffusional path length which the drug molecules have to traverse. The release of the drug from these gels are characterized by an initial phase of high release (burst effect) followed by a slower release as the gelation proceeds. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. Since the *in-situ* gelling systems are aqueous in nature the matrix formed before the complete gelation cross-linking is already be in a hydrated state there by circumventing the rate limiting step of matrix hydration in the initial stages.

The dissolution profile of all the batches revealed that concentrations of sodium alginate, calcium carbonate and gaur gum have an important role in drug release pattern. Among the 9 formulations evaluated, P1 which contained the lowest proportion of sodium alginate and calcium carbonate showed burst release with > 90 % drug released in about 6 h though gaur gum was also present in the formulation. On the other hand formulations P7, P8 and P9 which contained the highest proportion of sodium alginate, calcium carbonate with gaur gum displayed a gradual and sustained release over a period of 10 h.

Average effect of conc. of sodium alginate and calcium carbonate on % drug release of fenofibrate floating *in-situ* gel formulations of fenofibrate is presented in Table 11 along with Figure 11.

Table 11: Average effect of conc. of sodium alginate and calcium carbonate on % drug release of fenofibrate floating *in-situ* gel formulations

Name of Polymer	Polymer's Concentration	Formula for Calculating Average effect	Values as per formula	% drug release
Sodium alginate	1.00	(P1+P2+P3)/3	(95.41+89.11+84.11)/3	89.54
	1.50	(P4+P5+P6)/3	(69.12+64.99+62.07)/3	65.39
	2.00	(P7+P8+P9)/3	(56.14+54.17+50.39)/3	53.56
Calcium Carbonate	0.50	(P1+P4+P7)/3	(95.41+69.12+56.14)/3	73.55
	0.75	(P2+P5+P8)/3	(89.11+64.99+54.17)/3	69.42
	1.00	(P3+P6+P9)/3	(84.11+62.07+50.39)/3	65.52

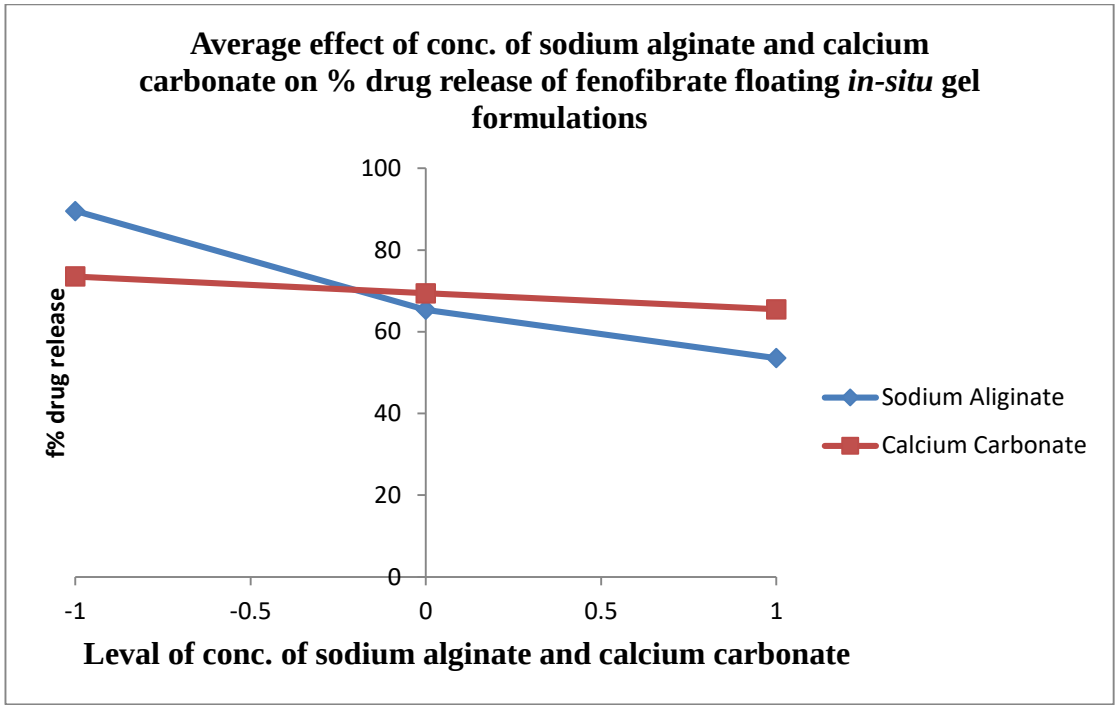

Figure 11: Average effect of conc. of sodium alginate and calcium carbonate on % drug release of fenofibrate floating *in-situ* gel formulations

Data was analysed by ANOVA and it was found that increase in conc. of sodium alginate from 1% to 2% resulted in significant ($P<0.05$; df= 2,6; $F_{crit}=5.14$; $F=57.06$) decrease in % drug release. However, increase in conc. of calcium carbonate from 0.5% to 1% resulted in insignificant ($P<0.05$; df= 2,6; $F_{crit}=5.14$, $F=5.14$) decrease in % drug release.

Main and interaction effects of independent variables on % drug release are shown in Figure 12 and 13 respectively.

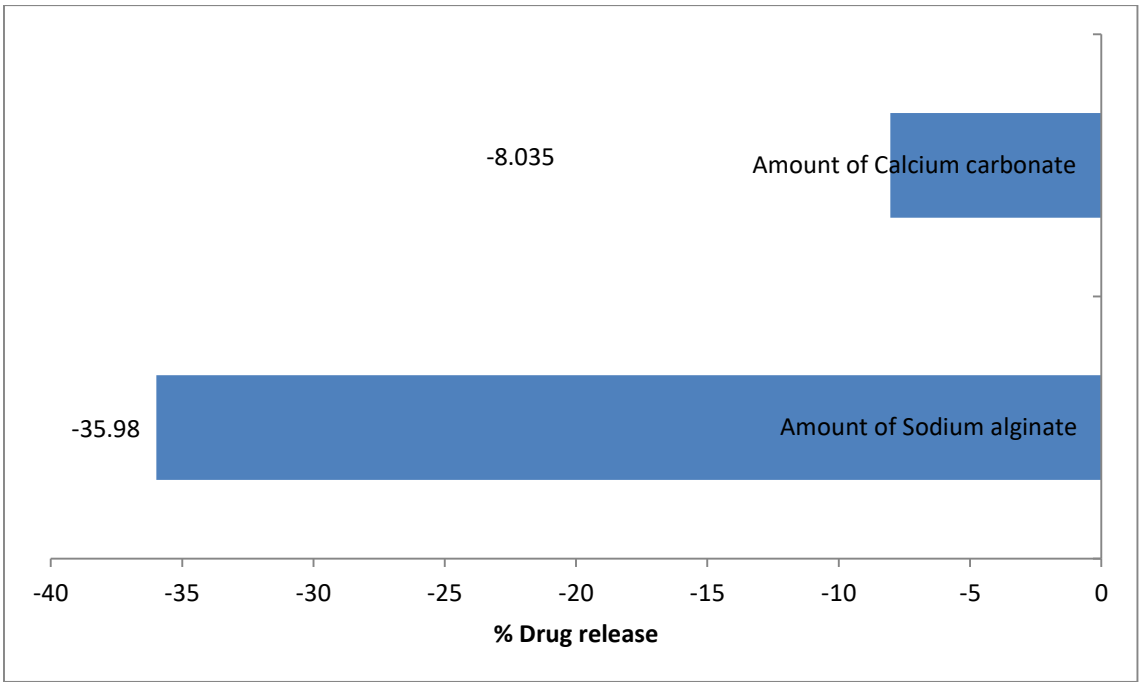

Figure 12: Main effect of conc. of sodium alginate and calcium carbonate on % drug release of fenofibrate floating *in-situ* gel formulations

Based on the main effect as shown in figure 6.24, out of the two parameters, conc. of sodium alginate influences % drug release to a greater extent.

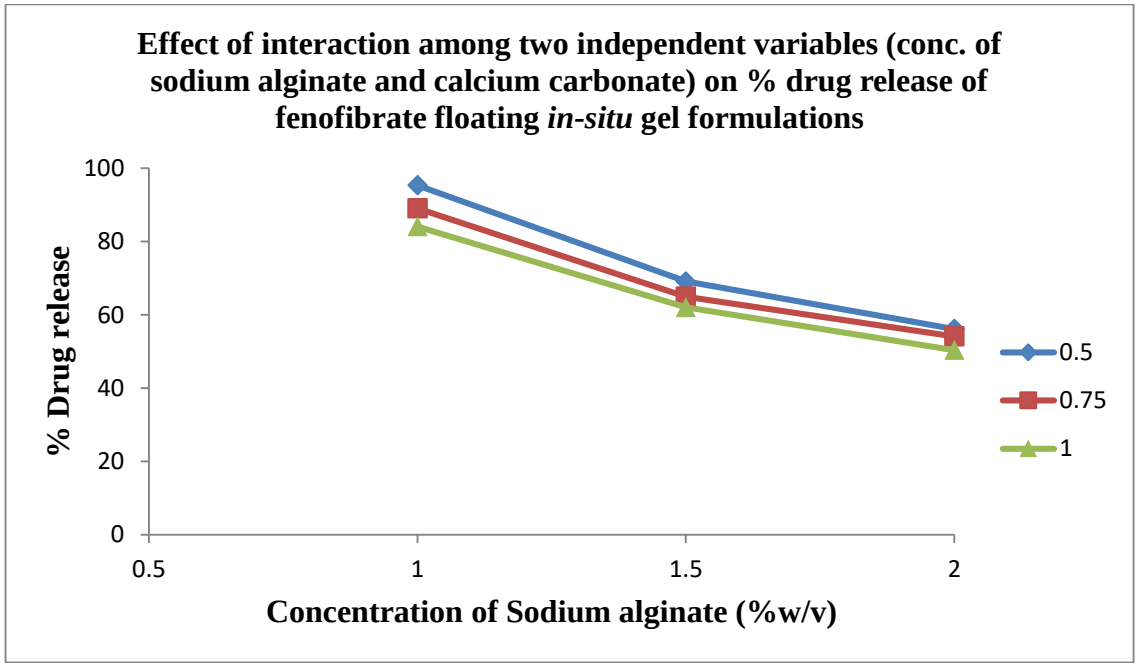

Figure 13: Effect of interaction among two independent variables (conc. of sodium alginate and calcium carbonate) on % drug release of fenofibrate floating *in-situ* gel formulations

Figure 13 shows a two dimensional plot showing the effect of interaction among the two variables (conc. of sodium alginate and calcium carbonate) on % drug release of the floating *in-situ* gel of fenofibrate. The relative slopes of lines within plot indicate if interaction is present. Parallelism of lines in figure 13 indicates interaction between concentration of sodium alginate and calcium carbonate.

CONCLUSION

Fenofibrate was successfully formulated in ion induced floating *in-situ* gelling system using Sodium alginate in combination with Calcium carbonate. It was seen that Sodium alginate is important for *in-situ* floating gel behavior along with calcium carbonate on the basis of main effect of concentration of sodium alginate and calcium carbonate. *In-vitro* results indicated that the *in-situ* floating gel system is a viable alternative to conventional oral dosage form by virtue of its ability to sustain drug release.

ACKNOWLEDGEMENTS

Authors are profusely thankful to B.N. University, Udaipur staff for their constant and perennial support.

REFERENCES

1. Pawar UK et al. “Gastro-retentive dosage forms: A review with special emphasis on floating drug delivery system”. Informa Healthcare USA, 2011; 18(2): 97-110.
2. Kale MT et al. “Oral floating controlled release drug delivery systems”. International Journal of Pharmaceutical Sciences Review and Research, 2011; 8(2): 106-111.
3. Shinde SR et al. “A novel approach of gastro-retentive drug delivery: In-situ gel”. Journal of Innovations in Pharmaceuticals and Biological Sciences, 2014; 1(1): 39-59.
4. Rathod HJ et al. “A review on stomach specific floating in-situ gel”. International Journal of Pharmaceutical Research, 2014; 6(4):19-30.
5. Bhardwaj L et al. “A short review on gastro retentive formulation for stomach specific drug delivery: Special emphasis on floating in-situ gel system”. African Journal of Basic & Applied Science, 2011; 3(6): 300-312.
6. Shaha SH et al. “An overview of a gastro-retentive floating drug delivery system”. Asian Journal of Pharmaceutical Science, 2009; 4(1): 65-80.
7. Vadgama N et al. “Gastro retentive in-situ gel formulation- A overview”. International Bulletin of Drug Research, 2013; 3(5): 69-82.
8. Shendge et al. “Novel strategy in controlled gastroretentive drug delivery: In-situ floating gel”. International Journal of Drug Delivery, 2014; 6(3): 230-243.
9. Tonnesen HH & Karlsen J. “Alginate in drug delivery system”. Drug Development and Industrial Pharmacy,2002; 28(6): 621-630.
10. http://www.fao.drug/docrep/w6355e/w6355e Ox.htm accessed on 30-08-2016.
11. Surendra T et al. “Guar gum: Present status and application”. Journal of Pharmaceutical and Scientific Innovation, 2013; 2(4): 24-28.

12. Kranthi KK et al. "Formulation and evaluation of floating in-situ gelling system of losartan potassium". Der Pharmacia Lettre, 2015; 7(1): 98-112.
13. Rao M et al. "Controlled release floating oral in-situ gel of itopride hydrochloride using pH sensitive polymer". International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(11): 338-343.
14. Thomas LM et al. "Formulation and evaluation of floating oral in-situ gel of metronidazole". International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(10): 265-269.
15. Jadav SL et al. "Formulation and evaluation of floating in-situ gel of nizatidine". International Journal of Research & Pharmaceutical Science, 2013; 4(2): 250-255.
16. Hunkeler D et al. "Gastro retentive drug delivery system for controlled drug release". United States Patent 20130315991; 2013.
17. Rajalakshmi R et al. "Development & Evaluation of a novel floating in-situ gelling system of levofloxacin hemihydrates". International Journal of Innovative Pharmaceutical Research, 2011; 2(1): 102-108.
18. Wamorkar V et al. "Formulation and evaluation of stomach specific in-situ gel of metaclopramide using natural, biodegradable polymers". International journal of Research in Pharmaceutical Science and Biomedical Science, 2011; 2(1): 193-201.
19. Patel JK et al. "Floating in-situ gel based on alginate as carrier for stomach specific drug delivery of femotidine". International Journal of Pharmaceutical Science and nanotechnology, 2010; 3(2): 1092-1104.
20. Asmussen B et al. "Gastroretentive system comprising an alginate body". United States Patent 20100129445; 2010.
21. Wataru K et al. "Oral sustained delivery of paracetamol from in-situ gelling gellan and sodium alginate formulation". International Journal of Pharmaceutics, 2003; 258: 55-64.
22. Miyazak S et al. "Comparision of in-situ gelling formulation for the oral delivery of cemitidine". International Journal of Pharmaceutics, 2001; 220: 161-168.
23. Deboeck M et al. "Stable controlled release pharmaceutical composition containing fenofibrate and pravastatin". United States Patent 20150037414; 2015.
24. Chattaraj SC et al. "Fenofibrate formulation" United States Patent 8722083; 2014.
25. Danki LS et al. "Design and in-vitro evaluation of gastric floating drug delivery system of fenofibrate". International Journal of Pharma and Bioscience, 2010; 1(2): 1-27.
26. Sarkar B et al. "Effect of sustained release solid dispersion on dissolution of poorly soluble drug". Asian Journal of Biomedical and Pharmaceutical Science, 2011; 1(2): 8-10.