FORMULATION AND INVITRO EVALUATION OF FLUVASATIN IN-SITU GELS.

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ABSTRACT

To increase the time that dosage forms remain in the stomach, gastro retentive drug delivery devices are frequently used. The floating in-situ gelling formulation, among the many strategies, offers prolonged stomach retention and sustained drug release, as well as the added benefit of liquid oral dose form. The goal of the current study was to create and assess a floating in situ fluvastatin gel employing a variety of polymers, including HPMC K4M, Gaur gum, and HPMC K15M, which undergo a pH-dependent sol-gel transition at gastric pH, extending the system's retention in the stomach. A natural polymer called sodium alginate was used as a gelling agent. Calcium carbonate, which is a source of calcium ions, causes gelation to occur. Polymers and drugs were tested FTIR studies were used to conduct a compatibility analysis on the samples, and the results showed no interaction between the drugs and the polymers. In vitro criteria such gelling nature, total floating time, medication content, viscosity, and in vitro dissolution studies were evaluated. Out of all the formulations, the F8 formulation including guar gum was selected as the most optimal formulation since it demonstrates maximum drug release after 12 hours and has outstanding floating and stomach retention properties. The improved formulation exhibits zero order release with a super case II transport mechanism according to kinetic experiments.

KEY WORDS: *In situ gel, pH-dependent sol-gel transition, Fluvastatin, Sodium alginate, Calcium carbonate, Guar gum, HPMC K4M, and HPMC K15M.*

INTRODUCTION:

In order to target site-specific drug release in the upper gastrointestinal tract for local or systemic effects, gastro retentive drug delivery is a strategy. Long-lasting gastro retentive dose forms can greatly extend the time that medications are retained in the stomach. Many techniques to gastro-retentive medication administration are now being studied and developed.

Effervescent systems: These buoyant delivery systems use matrices made of swellable polymers like Methocel or polysaccharides, like chitosan, and effervescent components, like sodium bicarbonate and citric or tartaric acid, or matrices having chambers of liquid that gasify at body temperature. By the volatilization of an organic solvent (such as ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate-bicarbonate salts, gas can be introduced into the floating chamber.

Noneffervescent systems: Non-effervescent floating drug delivery systems are typically made of polysaccharides that gel or swell readily or polymers that form matrices, such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate. One method involves the close mixing of the medication with a hydrocolloid that forms a gel upon contact with the stomach fluid following oral delivery and maintains a relative integrity of shape and a bulk density less than unity within the gastric environment. These medication formulations have buoyancy due to the air trapped by the inflated polymer. hydroxyl propyl methyl cellulose (HPMC), polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates are the excipients utilised most frequently in these systems.

Mechanistic floating in-situ gel

The medicine is removed from the system slowly and at the desired pace while it is floating on the stomach. In addition to the minimal gastric content required to properly implement the buoyancy retention principle after medication release, a minimal level of floating force (F) is also necessary to maintain the dose form reliably buoyant on the surface of the subject. An innovative apparatus for determining result weight has been documented in the literature to quantify the floating force kinetics. The equipment works by continually measuring the force required to lift a submerged object equal to F (as a function of time). If you place the object on the upper positive side, it will float better. This device aids in optimising FDDS with regard to the stability and longevity of the floating forces generated in order to avoid the negative effects of unpredictable intragastric buoyancy capability variations. F=Fbuoyancy-Fgravitation =(Df-Ds)gv Where F = total vertical force, Df = fluid density, Ds = object density, v = volume, and g = gravitational acceleration

in-situ gel:

Drug delivery methods that use in situ gel formation are, in theory, able to release drugs throughout time while keeping plasma concentrations relatively stable. These hydrogels are liquid at ambient temperature, but when they come into touch with bodily fluids or experience a pH change, they begin to gel. These are characterised by cation -induced gelation, temperature dependence, and pH dependence. Insitu forming drug delivery systems have potential benefits over conventional controlled release formulations, including convenience of

administration, decreased frequency of administration, greater patient compliance, and comfort. 1-2 Muco adhesive drug delivery systems include insitugel forming systems. Unlike extremely powerful gels, They are simple to apply in liquid form to the drug absorption site. They swell to form a solid gel at the site of medication absorption, which can extend the active substance's duration in the body. The creation of insitu gels can be accomplished using both organic and synthetic polymers. pH change, temperature variation, and ionic cross-linking are a few of the stimuli that can lead to in-situ gel formation. 3-5. Insitu gels are therefore supplied orally, topically, topically and vaginally, as well as intraperitoneally. Recent developments in insitu gels have made it possible to take advantage of the physiological variations in various GI tract regions for better drug absorption and patient convenience and compliance.

1.1Materials and Methodology:

Solubility studies:

Studies on fluvastatin's solubility were conducted in a variety of solvents, including 0.1N HCL, methanol, ethanol, 7.4pH buffer, and 6.8 pH buffer. Excess medication was added to the vehicles to create saturated solutions, which were then shaken continuously for 24 hours at 25°C to achieve saturation. Filtered samples (1 ml) were properly diluted with the right buffer, and the solubility of fluvastatin at 304 nm was evaluated spectrophotometrically**.**

Drug-excipient compatibility study:

In a mortar, physical mixes of the two ingredients were made by pulverising them in a certain order. A glass vial containing a sample weighing 3–4 grammes was filled with the sample, sealed with an aluminium cap, and labelled appropriately. For the initial assessment, samples were examined, their colours noted, and then loaded into stability chambers for 30 days at a temperature of 400 °C and a relative humidity of 75%. After 15 and 30 days, samples were taken out and checked for colour changes.

Determination of Absorption maxima by UV spectrophotometer:

A stock solution with a 1000 g/ml concentration was created by dissolving 10 mg of fluvastatin in 10 ml of buffers. From this solution, 1 ml was taken out and diluted to 10 ml to achieve a concentration of 100 g/ml (SS-II). To obtain a concentration of 10 g/ml from this stock solution, pipette out 1 ml of the solution and dilute it to a volume of 10 ml using buffer. The solution was then scanned using UV spectroscopy at a wavelength of 200–400 nm.

1.2. Fluvastatin calibration curve preparation:

10 mg of Fluvastatin were dissolved (at a 1000 g/ml concentration) in 10 ml of 0.1N HCL. With the addition of 0.1N HCl, 1 ml of this solution was brought up to 10 ml, yielding a concentration of 100 g/ ml (stock solution). Concentrations of 4, 8, 12, 16, 20 and 24 g/ml in 0.1N HCl were produced from the stock solution. At 304 nm, the absorbance of diluted solutions was measured, and the resulting data were used to create a standard plot. It was estimated the correlation coefficient.

1.3. Method of Preparation of *In-situ* Gel:

Fluvastatin floating in situ gel formulations were created utilising the table's ingredients.

Take a 100 ml beaker, add sodium alginate, polymer, and 60 ml of distilled water to it. Then, using a heated magnetic stirrer, heat the mixture at 60 °C until solution forms.Take a second 100 ml beaker, add calcium carbonate and sodium citrate, mix with 30 ml of distilled water, and boil at 60 °C until solution forms. Take a new beaker, add 5 ml of methanol and the medication, and then combine the three liquids at 60 °C. To obtain the final preparation, which was stored in amber colour bottles, mechanically agitate the aforementioned combination for 30 minutes after cooling it below 40°C.

Table : Formulation of Fluvastatin oral insitu gels

Ingredients (g)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Fluvastatin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	**0.5**
Sodium alginate	1	1	1	1	1	1	1	1	1	1	1	**1**
Calcium chloride (%w/v)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	**0.05**
Sodium citrate	170	170	170	170	170	170	170	170	170	170	170	**170**
HPMC K4M	0.2	0.4	0.6	0.8	--	--	--	--	--	--	--	**--**
Guar gum	--	--	--	--	0.2	0.4	0.6	0.8	--	--	--	**--**
HPMC K15M	--	--	--	--	--	--	--	--	0.2	0.4	0.6	**0.8**
Water (ml)	100	100	100	100	100	100	100	100	100	100	100	**100**

1.4. EVALUATION PARAMETERS OF ORAL IN-SITU GELS:70-79

Visual Appearance and Clarity:

Under fluorescent lighting, visual appearance and clarity were checked for the existence of any particle matter against a white and black background**.**

pH Measurement:

A pH metre was used to determine the pH of the produced in-situ gelling system after all the materials had been added.

Determination of drug content:

Measuring accurately 5 mL of formulation from various batches and transferring it to a 100 mL volumetric flask allowed for the determination of the drug content. This was mixed with 50–70 mL of 0.1 N HCL for 30 minutes using a sonicator. 100 mL were added to the volume. Visual inspection was used to guarantee complete dispersion of the contents, and Whattman

Filter Paper was used to filter the dispersion. 1 mL of the sample was taken out of this solution and diluted with 0.1 N HCL to make 10 mL. Using a UV-Visible Spectrophotometer, the contents of fluvastatin were determined at their highest absorbance at 304 nm. PG Instruments T60

In vitro floating study:

The in-vitro floating investigation was conducted by gently adding 5 mL of formulation to a beaker containing 100 mL of pH-1.2, 0.1N HCl at 37°C. The amount of time the formulation spent floating continuously on the dissolving medium's surface was noted.

In-vitro gelation study :

5 mL of the formulation, properly measured, was added to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2), at 37°C, in a beaker with gentle agitation to prevent breaking of the gel that had already formed.Depending on how stiff the formulation was, three classifications of in vitro gelling capacity were assigned.Gels quickly dissolve after a few minutes (+) Gelation immediately lasts for several hours (+++) Gelation immediately lasts for a considerable amount of time.

Measurement of viscosity of *in-situ* gelling system :

the dispersion's viscosity was measured using a Brookfield digital viscometer (NDJ-5S Viscometer). The samples (5 mL) were sheared on spindle number 2 at room temperature at a rate of 10 revolutions per minute. Each sample's viscosity was measured three times, with each measurement taking about 30 seconds.

1.5. *In-Vitro* Release Studies:

Studies on Drug Release in Vitro: Using USP Type II Paddle Type Equipment, the drug release investigation was conducted at 37 0.5oC and 50 rpm using 900 ml of 0.1 N HCl (pH 1.2). The test was conducted using in situ gel equivalent to 25 mg of fluvastatin. At regular intervals, sample solution (5 ml) was removed, filtered through a 0.45 m membrane filter, diluted, and appropriately examined by a UV spectrophotometric LABINDIA 8000 at 304 nm. As soon as the test sample was removed, fresh dissolving medium was added to keep the sink condition. For 12 hours, the dissolving studies were conducted.

1.6. RELEASE KINETICS:

To explain the release kinetics of fluvastatin from the insitu gels, data from the in vitro release were fitted to several equations and kinetic models in the current work. The kinetic models employed were the Higuchi release, Zero Order Equation, First Order, and Korsmeyer-Peppas models.

Kinetic Research: Models in mathematics:

To interpret the release rate of the drug from matrix systems for the optimised formulation, various release kinetic equations (zero-order, first-order, Higuchi's equation, and Korsmeyer-Peppas equation) were used. Calculated was the best match with the highest correlation (r2).

Zero-order model:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be representedby the equation

$Qt = Q0 + K0t$

Where Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time.

First Order Model:

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order equation:

$Log\ C = Log\ C_o - kt/2.303$

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

Higuchi model:

The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that

- initial drug concentration in the is much higher than drug solubility;
- drug diffusion takes place only in one dimension (edge effect must be negligible);
- drug particles are much smaller than system thickness;
- swelling and dissolution are negligible;
- drug diffusivity is constant; and
- Perfect sink conditions are always attained in the release environment.

In a general way the Higuchi model is simply expressed by following equation

$Q = K_H - t^{1/2}$

Where, K_H is the Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Korsmeyer-Peppas model:

Korsmeyer et al.(1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first60% drug release data were fitted in Korsmeyer-Peppas model,

$Mt / M\infty = Kt^n$

where $Mt / M\infty$ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

In this model, the value of n characterizes the release mechanism of drug as described in the following table.

Table No : Drug transport mechanisms suggested based on 'n' value.

S.No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

The results of *in vitro* release profiles obtained for the insitu gels formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first- order kinetic model).
3. Cumulative percent drug released versus square root of time (higuchi's model).
4. Log cumulative percent drug released versus log time (korsmeyer - Peppas equation)

RESULTS AND DISCUSSION

2.1. Saturation Solubility of Fluvastatin:

Solubility of Fluvastatin was determined in water, 0.1 N HCL, & 6.8 phosphate buffer and values obtained were noted in the table given below.

Table : Solubility studies of Fluvastatin in various solvents

Solvents	Solubility(µg/ml)
0.1 N HCL	0.356
6.8 pH buffer	0.759
Water	0.742

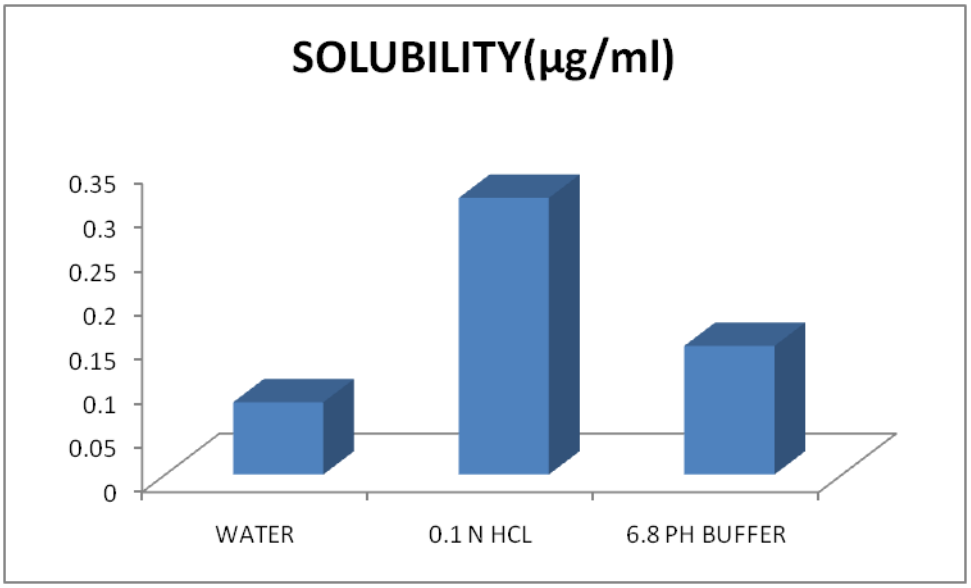

Fig : Solubility studies

From the above solubility data we can say that Fluvastatin has more solubility in 0.1N Hcl.

2.2.Compatibility study of Fluvastatin:

Compatibility between the drug and polymers was studied by FT-IR method. Pure Fluvastatin and optimized formulation were subjected for FT-IR spectroscopic analysis, to ascertain any interaction between the drug and polymers used. The position of characteristic peaks of pure Fluvastatin was compared with those peaks obtained for optimized formulation. These characteristic bands for Fluvastatin were identifiable and there was no major shift or disappearance in the peak positions.This indicated that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric network in the free form.

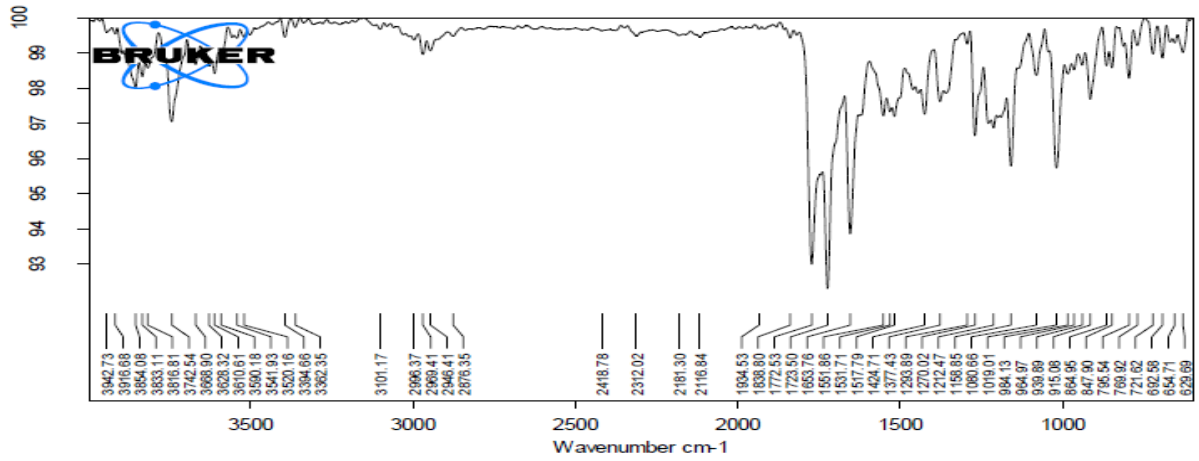

Fig FTIR graph of pure Fluvastatin

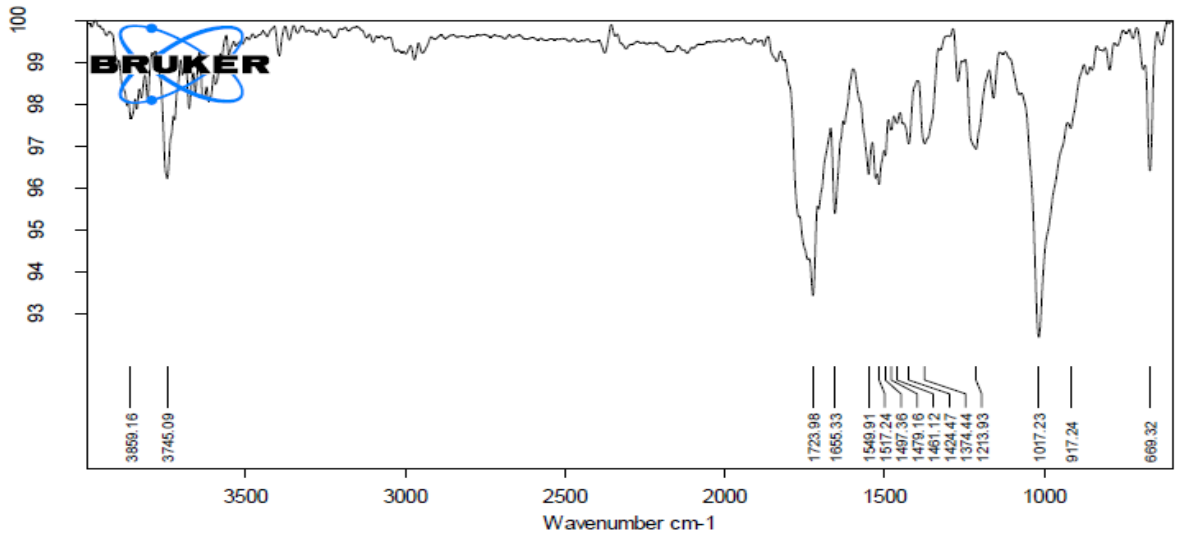

Fig FTIR graph of optimized formulation

2,3, Determination of absorption maximum (λmax) of Fluvastatin:

Determination of Fluvastatin λ-max was done for accurate quantitative assessment of drug .

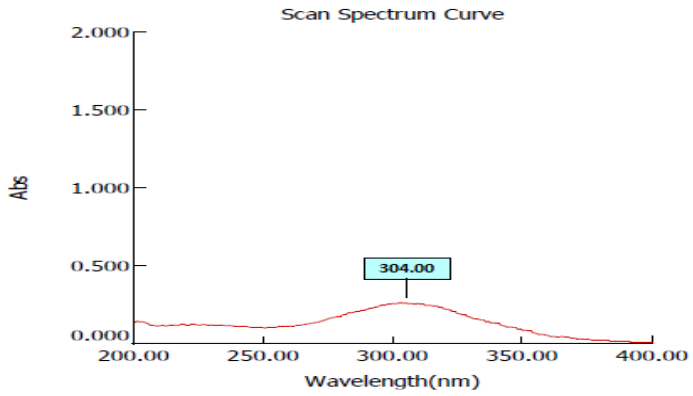

Fig :Absorption maximum (λ_{max}) of Fluvastatin 304 nm.

2.4. Standard calibration curve of Fluvastatin:

Table :Calibration curve dataFluvastatin in 0.1N HCl

Concentration (µg/ml)	**Absorbance**
0	0
5	0.124
10	0.248
15	0.372
20	0.496
25	0.612
30	0.744

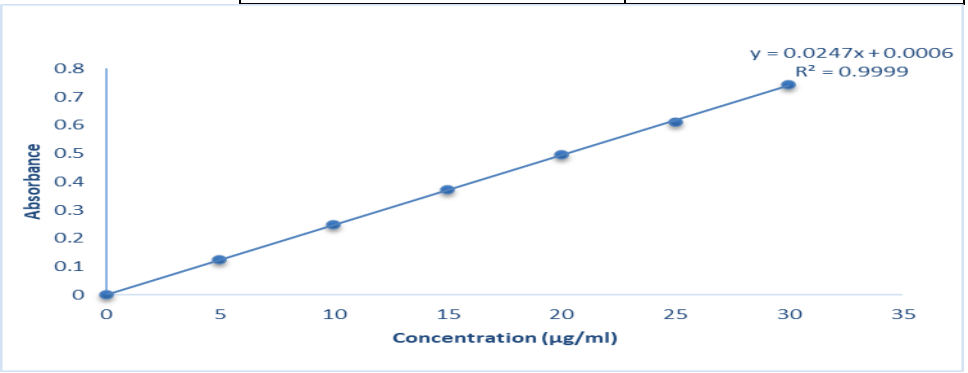

Fig:Calibration curve of Fluvastatin in 0.1N HCl

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Fluvastatin beer's range concentration was found to be in the range of 5-30 µg/ml using 0.1 N HCL buffer as buffer solution. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law as it was linear.

2.5. Drug content:

Table :Percentage Drug content of Fluvastatin insitu gels

Formulation code	Drug content(%)
F1	97.52
F2	98.26
F3	96.15
F4	99.42
F5	101.26
F6	98.04
F7	97.36
F8	99.04
F9	98.46
F10	96.50
F11	98.03
F12	100.12

The drug content was found to being the range of 94.4-98.8% for all the formulations indicating uniform distribution of drug.

2.5. In Vitro Gelation study

Gelling studies were carried out using 0.1N HCl and the obtained data were represented in Table. All formulations showed immediate Gelation upon contact with acidic medium and the formed gel preserved their integrity. Gelation occurs when the insoluble calcium carbonate solubilises when it comes in contact with acidic medium releasing carbon dioxide and calciumions. The calcium ions interact with the anionic polymer (sodium alginate) in the formulation causing instantaneous Gelation and provide a gel barrier that restricts drug release. Formulations containing calcium carbonate alone produce stiffer floating *in situ* gels than those containing $CaCO_3$. This is due to the internal ionotropic Gelation effect of calcium on sodium alginate.

Table : Invitro graded gel response data

FORMULATION CODE	GRADED GEL RESPONSE
F1	++
F2	++
F3	+++
F4	++
F5	++
F6	+++
F7	+
F8	++
F9	+++
F10	+
F11	++
F12	+

2.6. Viscosity studies

The formulation should have an optimum viscosity that will allow ease of administration and swallowing as a liquid and produces satisfactory gel strength for use as a delivery vehicle. The formulations showed a viscosity order of karaya gum <Xanthan gum <Guar gum. In addition to the influence of the type of viscosity enhancing polymer added, it was observed that increasing the concentration of the viscosity enhancing polymer in the formulation simultaneously increased the viscosity for all polymer types studied.

Table: Viscosity data

FORMULATION CODE	VISCOSITY (cps)
F1	298
F2	316
F3	335
F4	349
F5	361
F6	392
F7	215
F8	268
F9	301
F10	300
F11	150
F12	340

2.8. In vitro floating study:

The formulated floating *in situ* gelling system of Fluvastatin employed $CaCO_3$as a gas-generating agent. The *in vitro* floating test revealed the ability of all formulae to maintain buoyant for more than 12 h.

Table: Invitro floating Studies

Formulation code	Total floating Time (hr)
F1	~12
F2	~12
F3	~12
F4	~12
F5	~12
F6	~12
F7	~12
F8	~12
F9	~12
F10	~12
F11	~12
F12	~12

2.9. In vitro drug release study:

The *in vitro* release study of Fluvastatin from all formulations in 0.1N HCl was conducted for a period of 12 hours.

Table: In vitro drug release of Fluvastatin floating insitu gel

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	36.86	30.56	32.15	21.15	34.86	25.86	24.15	16.26	40.52	35.49	25.53	22.15
2	47.28	41.48	38.63	31.93	45.86	34.86	33.75	29.12	55.19	43.93	34.62	35.05
3	60.89	54.19	45.49	34.49	53.18	46.18	38.06	36.86	66.23	54.03	41.82	42.86
4	70.08	63.05	54.18	41.18	57.96	52.96	49.19	40.84	74.82	60.86	53.99	47.19
5	77.92	69.05	61.76	52.76	70.08	61.08	53.63	48.88	89.05	69.52	58.48	54.63
6	85.97	82.47	68.05	58.05	76.98	65.98	61.05	55.63	95.52	78.46	66.21	64.05
7	96.42	87.94	74.49	63.49	86.19	77.99	72.15	66.08		91.29	77.02	71.15
8		98.48	85.46	71.46	98.64	88.63	76.52	70.49		96.41	85.24	81.52
9			92.33	81.98		95.5	84.63	76.19			92.92	87.63
10			95.54	85.49			91.86	86.36			97.63	91.56
11				95.05			97.52	92.63				98.92
12								99.08				

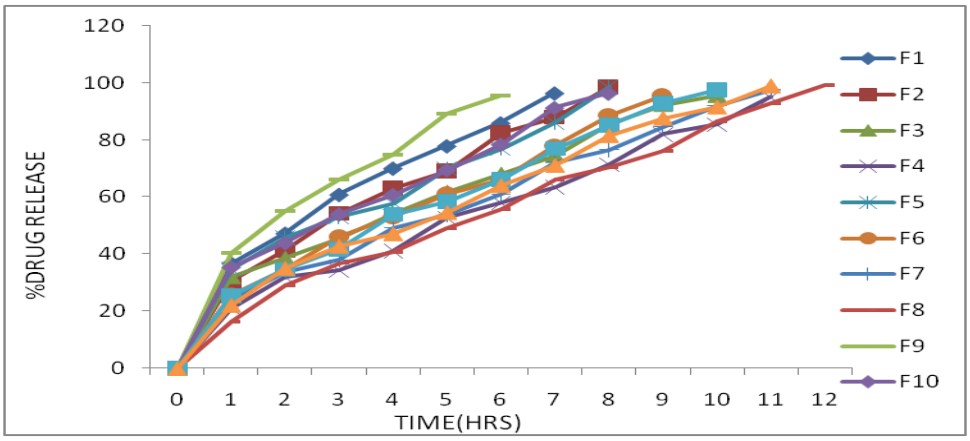

Fig: Invitro dissolution profile of F1-F12

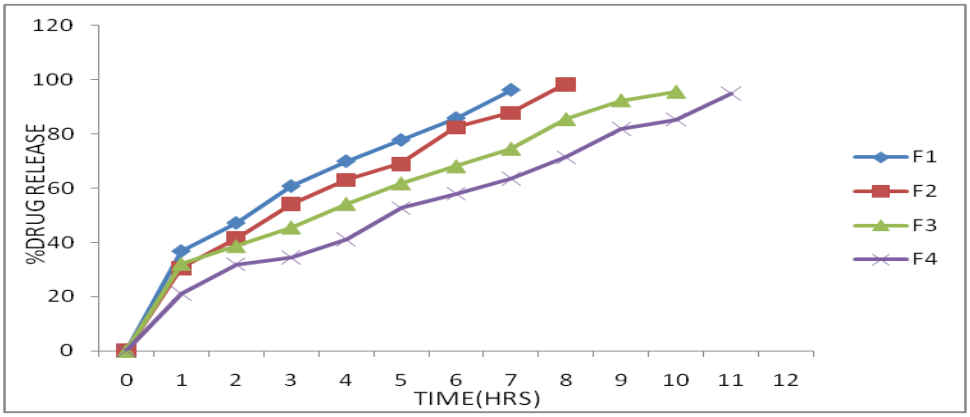

Fig:Invitro dissolution profile of F1-F4

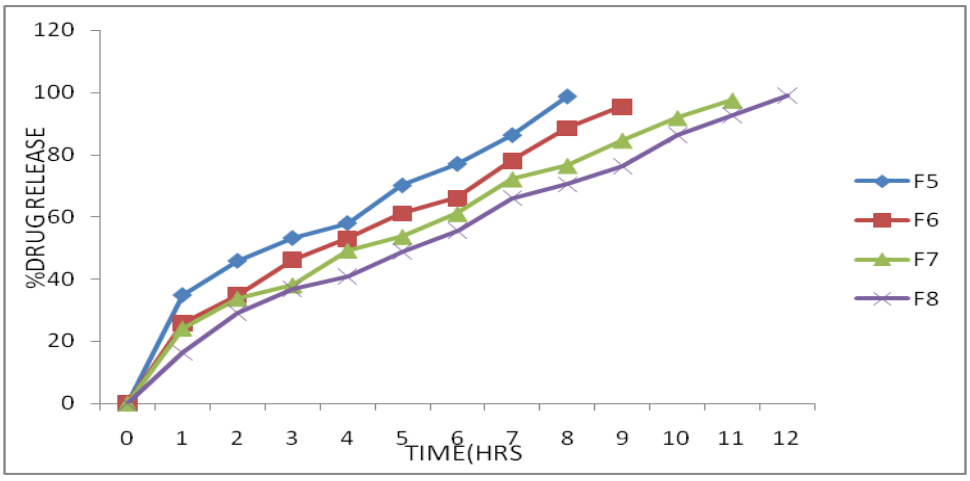

Fig: Invitro dissolution profile of F5-F8

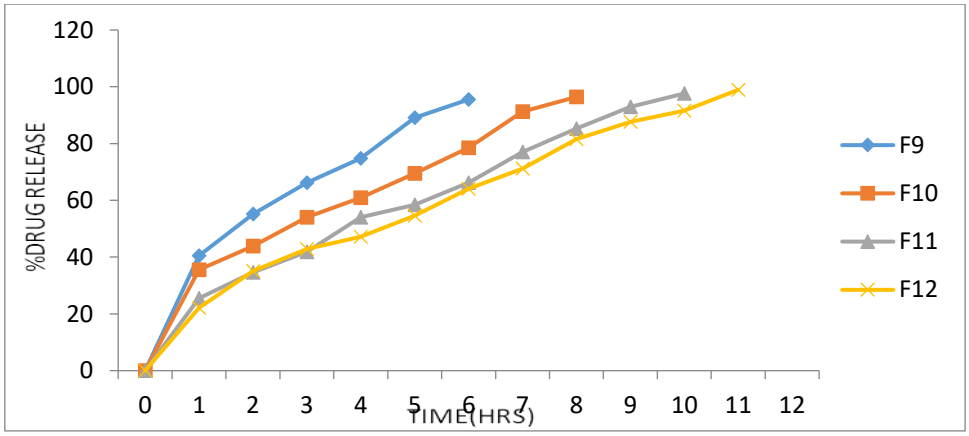

Fig: In vitro dissolution profile of F9-F12

From the in vitro drug release studies of Fluvastatin oral insitu gels using different polymer ratios.

Among the all 12 trails F1-F4 trails were formulated using HPMC K4M in four different ratios the drug release time was increased with increase in the polymer concentration. F1 formulation 96.42% of drug release at the end of 7hours, while F2 formulation shows 98.48% of drug release at the end of 8hours, While F3 formulation shows 95.54% of drug release at the end of 10 hours, whereas F4 formulation shows 95.05% of drug release at the end of 11 hours. Among all the four formulations cant sustained the drug release for 12hours. So further formulations were prepared using Guar gum.

Then F5-F8 trails were formulated using Guar gum in four different ratios, the drug release time was increased with increase in the polymer concentration. F5 formulation shows 98.64% of drug release at the end of 7hours, while F6 formulation shows 95.50% of drug release at the end of 8hours, while F7 formulation shows 97.52% of drug release at the end of 11 hours, whereas F8 formulation shows 99.08% of drug release at the end of 12 hours.Among all the four formulations F8 sustained the drug release for 12 hours. Further formulations were prepared using HPMC K15M.

Then F9-F12 trails were formulated using HPMC K15M in four different ratios. F9 formulation shows 95.52% of drug release at the end of 6hours, while F10 formulation shows 96.41% of drug release at the end of 8hours, while F11 formulation shows 97.63% of drug release at the end of 10hours, whereas F12 formulation shows 98.92% of drug release at the end of 11hours.Among all the four formulations cant sustained the drug release for 12hours.

Among the all 12formulations, based upon the invitro studies F8 formulation containing higher concentration of Guar gum choosen as optimized formulation, and has higher viscosity nature the formulation with higher concentration of Guar Gum maintains sustained drug release.

So the drug release kinetics were performed for the F8 formulation.

2.10.Drug release kinetic studies:

Zero order release kinetics:F8

Fig:Zero order release graph

First order release kinetics:F8

Fig: First order release graph

Higuchi release plot:

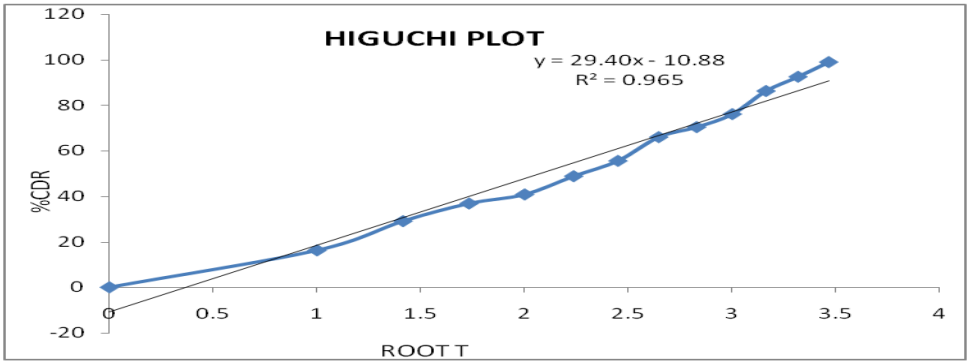

Fig: Higuchi release graph

Peppas release plot:

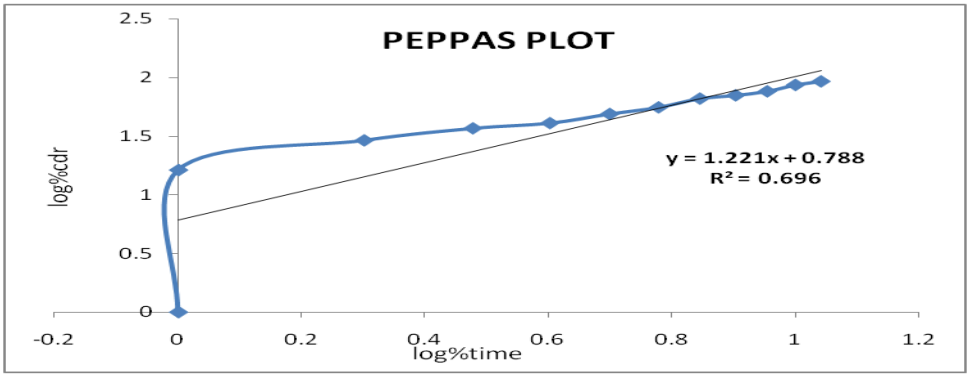

Fig:Peppas release graph

R^2 values					**n values**
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F8	0.986	0.750	0.965	0.696	1.221

The invitro dissolution data for best formulation F8 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.986. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The 'n' value is 1.221for the optimised formulation(F8) i.e., n value indicates super case II transport mechanism.The release kinetics for the optimized formula are shown in table.

CONCLUSION

Fluvastatin oral in-situ gelling systems were prepared by using polymers like Guar gum, HPMC K4M, HPMC K15M, Sodium citrate, Calcium carbonate and Sodium alginate. Total of twelve (F1 to F12) formulations were prepared and F8 was found to be the best formulation guar gum. Drug and polymers was subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drug and polymers. The prepared formulations were evaluated for drug content, floating lag time, total floating time, viscosity, gelling nature, visual appearance & invitro release studies were also performed. The invitro release studies of all the formulations among them F8 formulation containing guar gum shows drug release of 99.08% by the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model (R^2 =0.965) and showed zero order (R^2 =0.986) drug release with super case II transport mechanism.

From the above experimental results, it can be concluded that,

Fluvastatin was chosen as the model candidate for development of oral insitu gel, since they possess near ideal characteristics that these drugs must have formulating sustained drug delivery system.

The results of study demonstrate that guar gum was suitable to develop sustained release oral insitu gels.

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