FORMULATION DESIGN & DEVELOPMENT AND IN VITRO EVALUATION OF DYSLIPIDEMIA STATIN DRUG OF FLOATING ORAL IN SITU GELS USING pH DEPENDENT NATURAL POLYMERS BY SOL-GEL TRANSFER TECHNIQUE

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Abstract

Gastric retention drug delivery systems are widely used to prolong the residence time of dosage forms in the stomach. Floating-in situ formulations, among other approaches, provide longer drug release and gastric residence time with the advantages of oral liquids. This study sought to construct and evaluate floating in situ gels of fluvastatin using various polymers such as xyloglucan, locust bean gum, Gaur gum, Karaya gum which undergo a pH-dependent sol-gel transition at gastric pH, thereby extending shelf life. chewing gum. System in the stomach. Sodium alginate is a natural polymer used as a gelling agent in which gelling is initiated by the presence of calcium ions in the form of calcium carbonate. Studies on the relationship between drug and polymer using FTIR studies have shown that there is no interaction between drug and polymer. In vitro parameters such as gel properties, total swimming time, drug content, viscosity and in vitro dissolution were examined for analysis. Among all formulations, the F12 formulation containing bison gum was chosen as the optimized formulation showing the highest drug release at the end of 12 hours with good buoyancy properties and gastric retention. From kinetic studies, the formulation showed a zero-order release with a superstate II transport mechanism.

Keywords: gel in situ, pH dependent sol-gel transition, alginic acid, xanthan gum, karaya gum, xyloglucan, locust bean gum

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INTRODUCTION

Gel In-Place: The development of the in-situ gel system has received a lot of attention over the past few years. Gel-forming drug delivery systems that can continuously release drugs while maintaining constant plasma levels are essential. These hydrogels are liquid at room temperature but gel on contact with body fluids or changes in pH. The hydrogels showed temperature-dependent, pH-dependent and cation-induced gelling properties. Compared to controlled-release drugs, the on-site drug delivery system has advantages such as simple design, easy administration, reduced dose frequency, and improved patient compliance and comfort. The Insitugel-like delivery system is a mucoadhesive delivery system. Compared to very strong gels, they can be easily used in liquid form at the absorption point. At the drug absorption site, they swell to form a strong gel that increases the duration of the active drug. Both natural and synthetic polymers can be used to create in situ gels. In situ gel formation occurs due to a combination of one or more different stimuli such as pH change, temperature change, and ionic crosslinking. Thus, in situ gels are administered by oral, ophthalmic, rectal, vaginal and intraperitoneal routes. in situ gels. In consistent therefore not suitable for stomach pain reliever drug Ex: Aspirin and NSAIDs 1.3 Manufacturing process of gels in situ: Use or combine with various methods and techniques to produce gel in situ gel formation 8-12 Transplantation-In situ Gel This model deals with the phenomenon of flushing or diffusion. During swelling, polymers in the body absorb moisture from the surrounding environment and swell to form a viscous gel (such as glyceryl monooleate).Diffusion, diffusion of drugs and solvents in which the polymer dissolves or disperses into surrounding tissues, causing the polymer precipitate to form a gel (such as -methylpyrrolidone). Gel Formation Based on Chemical Changes or Stimuli: Changes in the body's chemical environment can cause gel formation by forming polymer cross-links. Ionic crosslinking In case of more than one ion in a liquid body, e.g. G. Na+, K+, Ca2+, Fe3+, etc., ion-sensitive polysaccharides such as pectin, pectin, etc., a phase change occurs due to the growth of crosslinks in the polymer, for example sodium alginate forms a gel in the presence of calcium chloride. Enzymatic crosslinking Enzymes found in body fluids can also cause crosslinking in polymer networks, which is considered the simplest type of gel formation. Forms Gels In Place Through Physiological Stimulants: Physiological stimuli that induce gel formation with include changes in temperature and changes in the pH system. In Situ Gel Formation In this way, temperature-dependent phase change from a low-viscosity solution to a high-viscosity gel can also be observed depending on the temperature change. Temperature changes cause rapid changes in the solubility of polymers in the body and polymer-polymer interactions occur or hydrophobic macromolecules are dissolved. Temperature sensitive polymers are most studied in in situ gel, for example Polyacrylic acid, polyacrylamide etc. Since there are many ionizable groups in the chemical structure of the polymer, the pH turns into a gel. Polymers with anionic groups show swelling with increasing pH, while polymers with cationic groups show swelling. Sensitive to Dilution This type of hydrogel contains polymers transferred to the bulk water phase. More polymer can be used by allowing the system to undergo a phase change due to dilution with water. TO.g:-LutrolF68 Electrical Signal Sensitive Current sensitive hydrogels are usually made of polyelectrolytes such as pH sensitive hydrogels. Electrosensitive hydrogels shrink or swell when exposed to electricity. Chitosan gel as matrix can be used for electrically modulated drug delivery Photosensitive hydrogel Photosensitive hydrogel can be used to form an in situ gel for engineering photosensitive artificial muscles or cartilage. Polymerizable functional groups such as ethyleosine and camphorquinone and their initiators can be injected into tissue and electrical energy used for gel formation by enzymatic treatment. For this reason. Use long UV wavelengths. Glucose Sensitive Intelligent stimulus-response systems using hydrogels capable of releasing insulin have been investigated. A cationic pH-sensitive polymer containing immobilized insulin and glucose oxidase swells in response to blood glucose levels and pulsatilely releases trapped insulin. Another way is to follow the competition between insulin or insulin and glucose for a stable site in concanavalin A, where insulin is released in response to glucose, so monitor insulin self-administration. Alternative methods from phenyl borate-poly (vinyl alcohol) polymers are also possible.1.4 In-situ Gel Mechanism of Action These are aqueous liquids prior to application, but are gel-like under physiological conditions. A few possible strategies for gel formation in situ are: -Ionic crosslinking, pH change and temperature change. Polymer solutions such as gellan gum, pectin, and sodium alginate contain divalent ions complexed with sodium citrate; These ions are

digested in the acidic environment of the stomach to release free divalent ions (Ca+2). It causes gelation of the oral solution in situ.It involves forming a double helix linkage region by joining two helical segments, combining with cations and water to form various linkages. 12-14 1.5 Methods Gastric Persistent Delivery Systems 15-21Gastric Persistent Drug Delivery is a method for prolonging residence time in the stomach for local or system effects through a specific zone of drug release to the upper GI. Stomach storage materials can stay in the stomach area for a long time, thus increasing the residence time of the drug in the stomach. Many gastric-holding drug delivery methods have been developed and improved. A. Floating drug delivery system (FDDS) Floating FDDS is an effective means of prolonging the residence time in the stomach to improve the bioavailability of the drug. FDDS is a low pressure system with enough buoyancy to float and stay in the stomach for a long time. The floating system can be divided into effervescent system and non-effervescent system.

Effervescent systems:

These floating delivery systems use matrices prepared from swellable polymers such as methylcellulose or polysaccharides; For example, chitosan and effervescent ingredients such as sodium bicarbonate and citric or tartaric acid, or matrices with liquid partitions that evaporate at body temperature. Gases, organic solvents (eg. For example, diethyl ether or cyclopentane) or the formation of carbon dioxide, such as the sulfide foaming reaction of organic acids and carbonate-bicarbonate. The matrix is designed in such a way that when carbon dioxide reaches the stomach, it is released by the acidity of the stomach contents and is retained in the gelled hydrocolloid. This creates an increase in paper quantity and maintains buoyancy. A floating pellet of the multi-unit type that produces carbon dioxide has recently been developed.

Non-effervescent systems:

Non-effervescent floating drug delivery systems are generally prepared from gel-forming or swellable polysaccharides or matrix-forming polymers such as polyacrylates, polycarbonates, polystyrenes, and polymethacrylates. In a way, the drug forms a hydrocolloid that is well mixed with the gel; this hydrocolloid comes into contact with gastric juice after oral administration and controls the relative shape and less than normal bulk density in the stomach area. The air trapped by the swelling of the polymer gives the bulk material buoyancy. Materials commonly used in these systems include hydroxypropyl methylcellulose (HPMC), polyacrylate, polyvinyl acetate, carbomer, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonate. 4Raft forming systems in contact with oil Gel-forming solutions (such as sodium alginate solutions containing baking soda or bicarbonate) expand and form viscous gels containing CO2 bubbles. This creates a layer on the stomach that slowly releases the drug in the stomach. This preparation usually contains antacids such as aluminum hydroxide or calcium carbonate to reduce stomach acidity. They are often used together with Liquid Gaviscon in the treatment of gastroesophageal reflux. C. Bioadhesive drug delivery systems Bioadhesive systems are systems that bind to the surface of gastric epithelial cells or mucins by transforming the drug into a biofilm. This strategy is based on GIT's self-defense system. Cytoprotective mucus is continuously secreted by specialized goblet cells throughout the GI tract. Bioadhesion is a bonding phenomenon in which organisms come together through mutual interaction. Links can be between man-made products and biological products, such as polymers and biofilms. The term mucoadhesion is used when the polymer attaches to the mucin layer of the mucosal tissue. Mucous membranes cover many parts of the body, including the gastrointestinal tract, ears, nose, and eyes. Therefore, they represent attachment points for the bioadhesive system.

2. MATERIALS AND PROCEDURES

Materials: All materials (AR grade) used in were obtained from various sources.

Experimental study (methodology)

Preformulation studies [14-25]

Solubility Studies:

The solubility of fluvastatin was performed in different solvents such as 0.1N HCL, methanol, ethanol, 7.4 pH buffers and 6.8 pH buffers. Prepare saturated solution by adding excess solution to vehicle and shaking on shaker for 24 hours at 25°C under continuous agitation. The filtered sample (1 ml) was suitably diluted with a buffer and the solubility of fluvastatin was determined spectrophotometrically at 267 nm.

Drug-excipient compatibility studies:

a) Preparation of physical drug and excipient mixture by grinding drugs and excipients in certain proportions in a pestle. Collect 3-4 g of sample in glass bottles, seal with rubber stoppers,

cap with aluminum cap and label appropriately. The samples were evaluated and color recorded for initial assessment and the samples were placed in a stable environment at 400°C and 75% RH for 30 days to examine the relationship. After 15 and 30 days, remove the sample and observe the color change. b) FTIR Spectroscopy The physical consistency of the pure drug and the polymer used in the study was tested by infrared (IR) spectroscopy. Fourier transform infrared absorption spectra of pure substances and physical mixtures were recorded with potassium bromide disk technique in the range of 400-4000 cm-1 using a Fourier transform infrared spectrophotometer.

Determination of maximum absorbance by UV spectrophotometer:
10 mg of fluvastatin was dissolved in 10 ml of insufficient solution to obtain a stock solution at a concentration of 1000 µg/ml. Extract 1 ml of this solution and dilute to 10 ml to achieve a concentration of 100 µg/ml (SS-II).Take 1 ml of this solution and increase the volume to 10 ml without achieving a concentration of 10 µg/ml, scan the solution under the UV spectrum using 200-400nm.

Preparation of fluvastatin calibration curve:
Dissolve 10 mg of fluvastatin (1000 µg/ml) in 10 ml of 0.1N HCL with gentle shaking. Take 1 ml of this solution and make up to 10 ml with 0.1N HCl to achieve a concentration of 100 µg/ml (Stock solution). From solutions of 4, 8, 12, 16, 20 and 24 µg/mlin 0.Prepare IN HCI. Measure the absorbance of the diluted solution at 267 nm and use the obtained data to plot the standard image. Calculate the correlation coefficient.

Preparation of the in situ gel:
The fluvastatin floating in situ gel prep was prepared using the ingredients in the table. Use 100ml beaker, take sodium alginate into beaker and add polymer, then mix with 60ml distilled water, heat. The mixture is heated at 60 °C to melt using a heated magnetic stirrer. Take another 100 ml beaker, add sodium citrate and calcium carbonate into it, then mix with 30 ml of distilled water and heat the mixture at 60°C until dissolved. Another beaker is taken, 5 ml of methanol is added and the three mixtures are mixed at 60°C. After the solution is cooled below 40°C, the above mixture is mixed together for 30 minutes to obtain the final preparation, which is stored in a container. amber bottle for future use.66-69 2.2.3

Evaluation of oral in situ gels: 70-79

Visual Appearance and Clarity:
Visual appearance and clarity were performed under fluorescent light against a white and black background to check small objects.

pH measurement:
After all components were added, the pH of the base gel system prepared with was measured using a pH meter.

Determination of solution content:
Accurately weigh 5 mL of the different components of the preparation and transfer to a 100 mL metered bottle. Add 50-70 mL of 0.1N HCL to it and sonicate for 30 minutes. Set the volume to 100 mL. Make sure the content is completely dispersed and pass the dispersion through Whattman filter paper. Take a sample of 1 mL of this solution and dilute to 0.0 to 10 mL.4 in vitro flotation studies in vitro flotation studies were performed without mass interaction by adding 5 mL of sample to a beaker containing 100 ml of 0.1N HCl (pH 1.2) at 37 °C. The amount of dissolution medium (floating time) is recorded for the time the formulation remains floating on the surface.

In vitro gelation study:
To measure the in vitro gelling ability of the sample, add 5 mL of accurately measured sample to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2) in a beaker at 37 °C, mixing gently, gel prevent the formation from breaking. In vitro gelling capacity is divided into three groups according to the difficulty of formation. (+) forms a gel after a few minutes and quickly degrades (++) gel to (+++) gel for a long time. 6.2.3.6 Measurement of Viscosity of an In-situ Gelation System The viscosity of the dispersion was measured using a Brookfield digital viscometer (NDJ-5S viscometer). Sample (5 mL) at room temperature No. 2 rotors at 10 rpm/min. Viscosity measurements for each sample were made in triplicate and each measurement was approximately 30 s.

In Vitro Release Studies:
Drug release studies were performed using a USP Type II paddle apparatus using 900 ml of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C and 50 rpm.An in situ gel equivalent to 25 mg of fluvastatin was used for the test. The sample solution (5 ml) was removed from the pre-order, filtered through a 0.45 µm membrane filter, diluted and

appropriately analyzed with the 267 nm UV spectrophotometer LABINDIA 8000. to throw. Explosive research was conducted for 12 hours.

Saturation Solubility of Fluvastatin:
The solubility of fluvastatin in water, 0.1 N HCL and 6.8 phosphate buffered saline, the results obtained are shown in the table below.

RESULTS AND DISCUSSION

Table.No.1: Solubility studies of Fluvastatin in various solvents

Solvents	Solubility(µg/ml)
6.8 pH buffer	0.356
0.1 N HCL	0.782
Water	0.721

Table.No.2 : Calibration curve dataFluvastatin in 0.1N HCl

Concentration(µg/ml)	Absorbance
0	0
5	0.136
10	0.268
15	0.399
20	0.532
25	0.664

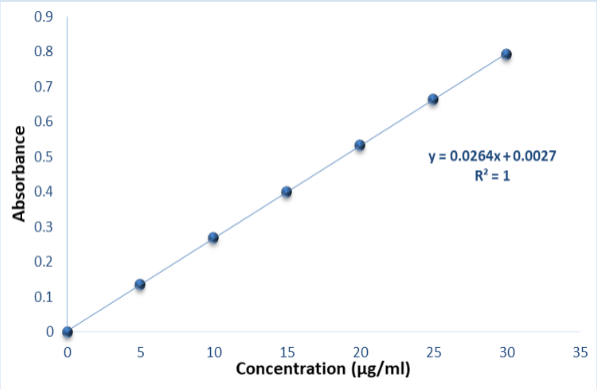

Figure.No:01 . Calibration curve of Fluvastatin in 0.1N HCl

Drug & Excipient compatibility:
Examining the relationship between fluvastatin Fourier transform infrared spectroscopy was used to examine the relationship between drug and polymer. FT-IR spectroscopic analysis of pure fluvastatin and optimized formulations was performed to identify any interactions between the drug and the polymers used. The peak properties of pure fluvastatin were compared with those obtained for the formulation. The characteristic bands of fluvastatin can be identified and there is no significant change or disappearance of the peak. This indicates that the drug is not good and does not react with the excipients used in the formulation, that is, they are compatible. Therefore, it can be concluded that the drug is in the Free State and can be easily released from the polymer network in free form.

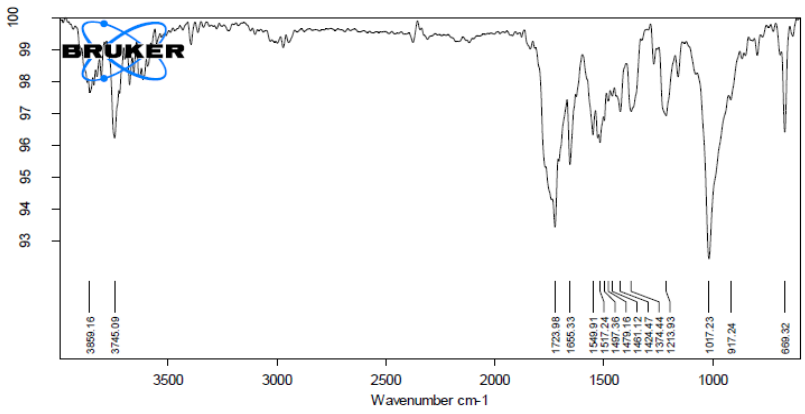

Figure.No.2 FTIR graph of optimized formulation

Determination of the maximum absorption (λmax) of fluvastatin:

Determination of the λ-max of fluvastatin is to measure the accuracy and quantity of the drug.

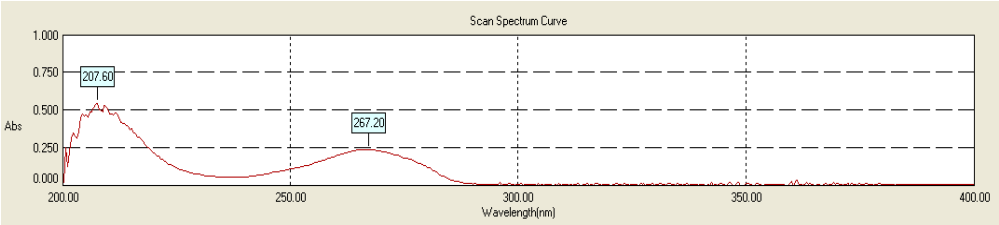

Figure.No.3: Absorption maximum (λ_{max}) of Fluvastatin267nm.

In vitro gelation studies:

Using gelation studies 0.1N HCl and the data obtained are listed in the table. All formulations exhibit immediate gelation when exposed to acid and the resulting gels retain their integrity. Gelation occurs when insoluble calcium carbonate dissolves in contact with an acidic environment, which releases carbon dioxide and calcium ions. Calcium ions interact with the anionic polymer (sodium alginate) in the formulation, increasing the gelling time and providing a gel barrier that limits drug release. Calcium carbonate-only formulations produced gels that floated more firmly in place than formulations containing CaCO3.This is due to the internal ionic gelation of sodium alginate by calcium.

Table.No.3.: Invitro graded gel response data

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

Viscosity Study:

The formulation should have the best viscosity for ease of application and swallowing as a liquid and satisfactory strength for use as an application tool. The formulations showed a viscosity order of gum karaya < xanthan gum < guar gum. In addition to the effect of the additional tackifying polymer, it was found that increasing the tackifier polymer concentration in the formulation simultaneously increased the viscosity of all polymer types studied.

Table.No.4: 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	302
F11	324
F12	398

In vitro floating study:
Fluvastatin floating-in situ gelling system developed in using CaCO3 as the gas-forming agent. The in vitro flotation test demonstrates the ability of all formulations to remain within 12 hours.

Table.No.5: 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

In vitro drug release studies:
In vitro release studies of fluvastatin were performed from all samples in 0.1N HCl for 12 hours.

Table.No.6: In vitro drug release of Fluvastatin floating insitu gel {F1-F12}

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	37.46	35.56	30.15	26.15	39.86	26.46	24.15	18.76	45.52	35.49	27.23	**24.15**
2	49.58	45.48	39.63	29.93	46.86	36.26	35.75	27.42	58.19	47.93	36.82	**33.05**
3	58.79	54.19	47.49	35.49	59.18	44.48	42.06	34.56	67.23	56.03	43.72	**40.86**
4	69.58	66.05	55.18	45.18	65.96	50.76	48.19	42.14	78.82	65.86	51.49	**49.19**
5	78.82	75.05	62.76	52.76	75.08	59.48	58.63	49.48	89.05	74.52	60.78	**56.63**
6	87.37	82.47	70.05	58.05	82.98	67.18	65.05	56.63	98.52	82.46	68.31	**65.05**
7	99.72	88.94	76.49	66.49	96.24	76.79	76.15	64.28		90.29	75.62	**72.15**
8		97.48	83.46	74.46		86.73	80.52	71.89		98.41	83.84	**79.52**
9			90.33	80.98		97.12	88.63	78.29			90.12	**86.63**
10			98.54	87.49			93.86	84.36			99.23	**93.56**
11				98.05			99.22	90.53				**96.92**
12								98.28				**99.75**

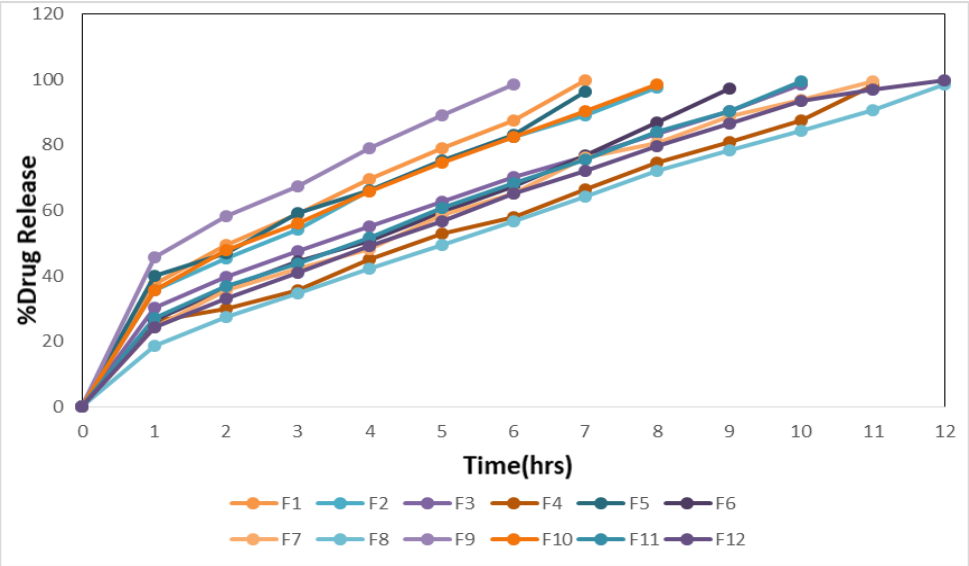

Fig No.4: In vitro drug release of Fluvastatin floating insitu gel {F1-F12}

Drug release kinetic studies:

Zeroorder release kinetics:F12

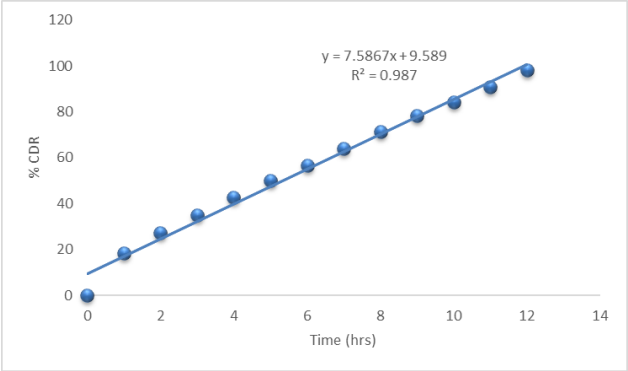

Fig: Zero order release graph

First order release kinetics:F12

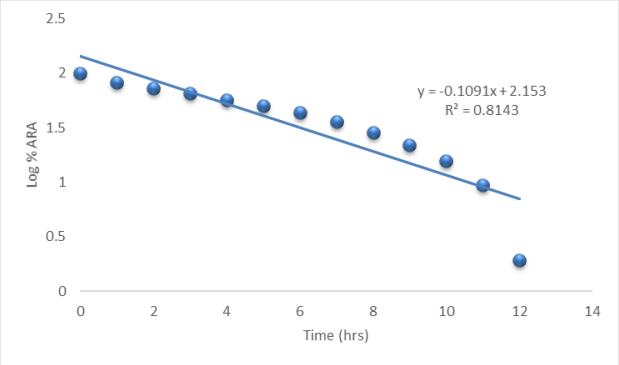

Fig: First order release graph

Higuchi release plot:

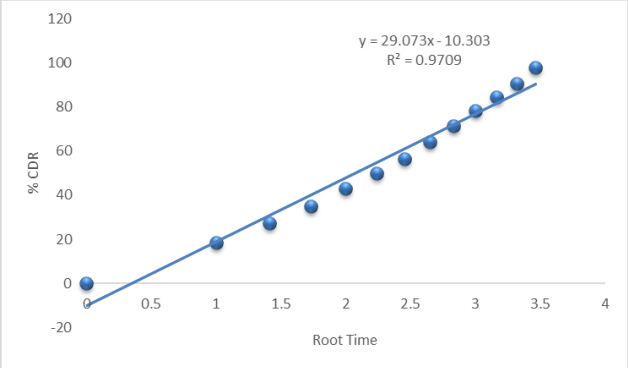

Fig: Higuchi release graph

Peppas release plot:

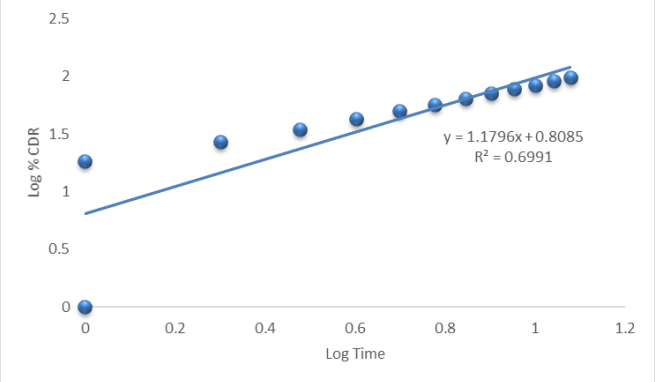

Fig: Peppasrelease graph

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F12	**0.987**	**0.814**	**0.970**	**0.699**	**1.180**

The invitro dissolution data for best formulation F8were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.987. 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 1.180for the optimised formulation (F12) i.e., n value indicates super case II transport mechanism. The release kinetics for the optimized formula are shown in table.

SUMMARY AND CONCLUSION

oral in-situ gelling systems containing drug Fluvastatin were prepared by using natural polymers like Alginic acid (E 400) , Calcium chloride, sodium citrate, Guar gum, xyloglucan, locust bean gum, Xanthane gum, Karaya gum, Povidone. Total of twelve (F1 to F12) formulations were prepared and F12 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 F12formulation containing guar gum shows drug release of 98.08% by the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model (R^2 =0.971) and showed zero order (R^2 =0.987) 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 possesses 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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