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A novel *in-situ* gel approach for sustained release of eplerenone

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Abstract
The present study was an attempt to formulate and evaluate floating *in-situ* gel of Eplerenone by using various polymers like Xanthan gum, Guar gum and Karaya gum which undergoes pH dependent sol-gel transition at gastric pH, there by prolonging the retention of the system in stomach. Sodium alginate a natural polymer was employed as a gelling agent where gelation is triggered by the source of calcium ions in the form of calcium carbonate. Drug and polymers was subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drug and polymers. The evaluation was carried out for *in vitro* parameters such as gelling nature, Total floating time, drug content, viscosity, & *in vitro* dissolution studies. Among all the formulations, F6 formulation containing guar gumwas chosen as optimized formulation which shows maximum drug release by the end of 12hrs and has excellent floating characteristics and gastric retention. From kinetic studies the optimized formulation shows zero order release with super case II transport mechanism.

Keywords: *In-situ* gel, pH dependent sol-gel transition, Gastro-retentive drug delivery systems, floating *in-situ* gelling, sustained drug release

Introduction
Eplerenone 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 primary requirement of a successful sustained release product focuses on increasing patient compliance which the *in-situ* gels offer. It provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in-situ gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the in-situ gel formulations can make them more acceptable and excellent drug delivery system.
In-situ drug delivery provides a greater potential for the development of liquid orals for their sustained drug release. This floating in-situ gel approach is suitable for drugs having narrow absorption window in stomach or drugs showing local effect in stomach. Eplerenone due to its shorter half life of 4- 5 hrs has to be sustained in the body so to prolong its release in the body it has been developed as *in- situ* gel by using various polymers.

Materials and Methods
Materials
All materials (AR Grade) used were obtained from different sources. Eplerenone was obtained as a gift sample from Hetero Labs Ltd, Hyderabad, sodium alginate was purchased from Color cone Asia Ltd., Verna, Goa, xanthan gum, calcium carbonate, sodium citrate, guar gum, karaya gum was purchased from MJ Biopharmaceuticals, Mumbai.

Preformulation Studies [20-23]
Solubility studies
Solubility of Eplerenone was carried out in different solvents like 0.1N HCL, Methanol, Ethanol, 7.4pH buffer and 6.8pH buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Eplerenone was determined spectrophotometrically at 267nm.

a) Drug-excipient compatibility study
Physical mixtures of drug and excipients were prepared by grinding specific ratios of drug and excipients in a mortar. Sample of 3-4 grams was loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap and labeled properly. Samples were observed and colour was recorded for initial evaluation and loaded into stability chambered at 40^0C temperature and 75% relative humidity for 30 days to study the Compatibility study. Samples were removed after 15 days and 30 days and observed for any change in the color [24].

b) FTIR spectroscopy
The physical compatibility between the pure drug and polymers used in the research was tested by Infra-Red (IR) spectroscopy. FTIR absorption spectra for pure drug and physical mixture were recorded in the range of 400-4000cm $^{-1}$ by KBr disc method using FTIR spectrophotometer.

Determination of Absorption maxima by UV spectrophotometer
10mg of Eplerenone was dissolved in 10ml of buffers so as to get a stock solution of 1000 µg/ml concentration. From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml (SS-II). From this stock solution pipette out 1 ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of calibration curve of Eplerenone [25-27].
10 mg of Eplerenone was dissolved in 10 ml of 0.1N HCL by slight shaking (1000 µg/ml). 1 ml of this solution was taken and made up to 10 ml with 0.1N HCl, which gives 100 µg/ ml concentration (stock solution). From the stock solution, concentrations of 4,8,12, 16, 20and 24µg/ml in 0.1N HCl were prepared. The absorbance of diluted solutions was measured at 267nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated.

Method of preparation of *in-situ* gel
Floating *in-situ* gel formulations of Eplerenone were prepared using compositions. Take 100ml beaker, in that beaker take sodium alginate and add with polymer, then mix with 60ml distilled water, now heat the mixture at 60 °C till solution occurs using a heating magnetic stirrer. Take another 100ml beaker, in this add sodium citrate along with calcium carbonate, then mix with 30ml distilled water, heat the mixture at 60 °C till solution occurs. Now take another beaker, add 5ml methanol with drug, then three mixtures are mixed at 60°C. After cooling this solution below 40 °C, keep the above mixture in mechanical stirring for 30 minutes, well to get the final preparation which was stored in amber colour bottles until further use [28-31].

Table 1: Formulation of Eplerenone oral *in-situ* gels

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eplerenone	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
Calcium carbonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan gum	0.25	0.5	0.75	--	--	--	--	--	--
Guar gum	--	--	--	0.25	0.5	0.75	--	--	--
Karaya gum	--	--	--	--	--	--	0.25	0.5	0.75
Water (ml)	100	100	100	100	100	100	100	100	100

Evaluation parameters of oral *in-situ* gels [32-42]
Visual Appearance and Clarity
Visual appearance and Clarity was done under fluorescent light against a white and black back ground for presence of any particulate matter.

pH Measurement
The pH of the prepared *in-situ* gelling system after addition of all the ingredients was measured using pH meter.

Determination of drug content
Accurately 5mL of formulation from different batches was measured and transferred to 100 mL volumetric flask. To this 50-70mL of 0.1 N HCL was added and sonicated for 30 min. Volume was adjusted to 100mL. Complete dispersion of contents was ensured visually and the dispersion was filtered using Whattman Filter Paper. From this solution, 1 mL of sample was withdrawn and diluted to 10mL with 0.1 N HCL. Contents of Eplerenone was measured at maximum absorbance at 267 nm using UV-Visible Spectrophotometer. [T60 PG INSTRUMENTS]

***In-vitro* floating study**
The *in-vitro* floating study was carried out by introducing 5 mL of formulation into a beaker containing 100 ml of 0.1N HCl, (pH 1.2) at 37°C without much disturbance. The time the formulation constantly floated on surface of the dissolution medium (duration of floating) were recorded.

***In-vitro* gelation study**
To evaluate the formulations for their in-vitro gelling capacity, accurately measured 5 mL of formulation was added to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2) at 37°C in a beaker with mild agitation that avoids breaking of formed gel.
The *in vitro* gelling capacity was graded in three categories on the basis of stiffness of the formulation.
(+) Gels after few minutes, dispersed rapidly
(++) Gelation immediate remains for few hours
(+++) Gelation immediate remains for an extended period.

Measurement of viscosity of *in-situ* gelling system
Viscosity of the dispersion was determined using a Brookfield digital viscometer (NDJ-5S Viscometer). The samples (5 mL) were sheared at a rate of 10 rpm/min using spindle number 2 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 seconds.

***In-Vitro* Release Studies**
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 0.1 N HCl (pH 1.2). In situ gel equivalent to 25 mg of Eplerenone was used for the test. Sample solution (5ml) was withdrawn at pre-determined time intervals, filtered through a 0.45µm membrane filter, diluted and suitably analysed by UV spectrophotometric LABINDIA 8000 at 267 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 12 h [43-50].

Release Kinetics [51-52].

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of Eplerenone from the *in-situ* gels. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r^2) was calculated.

Results & Discussion

Solubility studies of Eplerenone

Solubility of Eplerenone was determined in water, 0.1 N HCL, & 6.8 phosphate buffer and values obtained were noted in the table 2 given below. From solubility studies in various solvents eplerenone showed more solubility in 6.8pH buffer and methanol among the organic solvents.

Table 2: Solubility studies of Eplerenone in various solvents

Solvents	Solubility (µg/ml)
0.1 N HCL	0.356
6.8 pH buffer	0.759
7.4pH buffer	0.742
Methanol	1.968
Ethanol	0.968

Compatibility study of Eplerenone

Compatibility between the drug and polymers was studied by FT-IR method. Pure Eplerenone and optimized formulation were subjected for FT-IR spectroscopic analysis, to as certain any interaction between the drug and polymers used. The position of characteristic peaks of pure Eplerenone was compared with those peaks obtained for optimized formulation. These characteristic bands for Eplerenone 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.

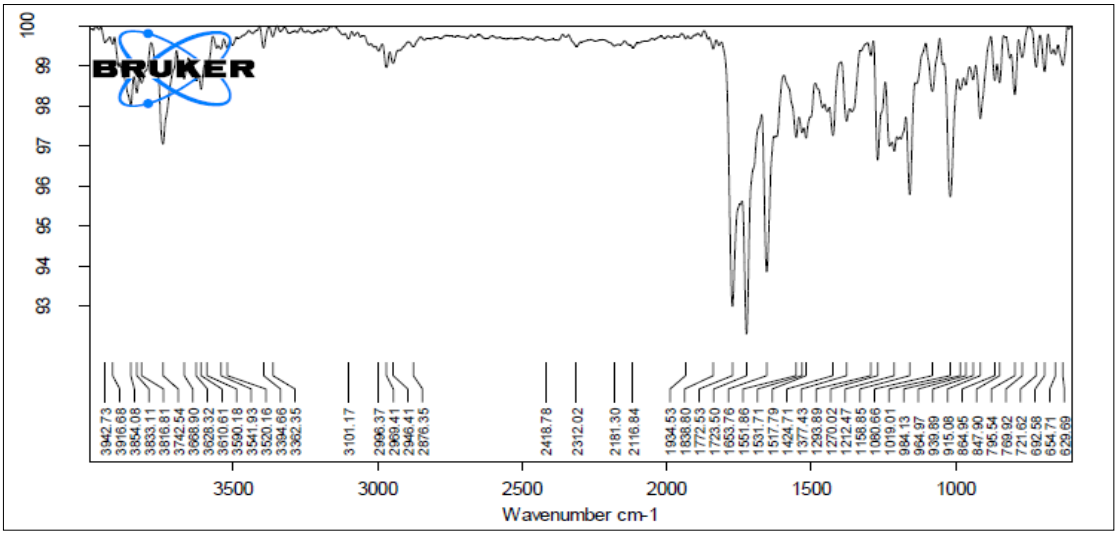

Fig 1: FTIR graph of pure Eplerenone

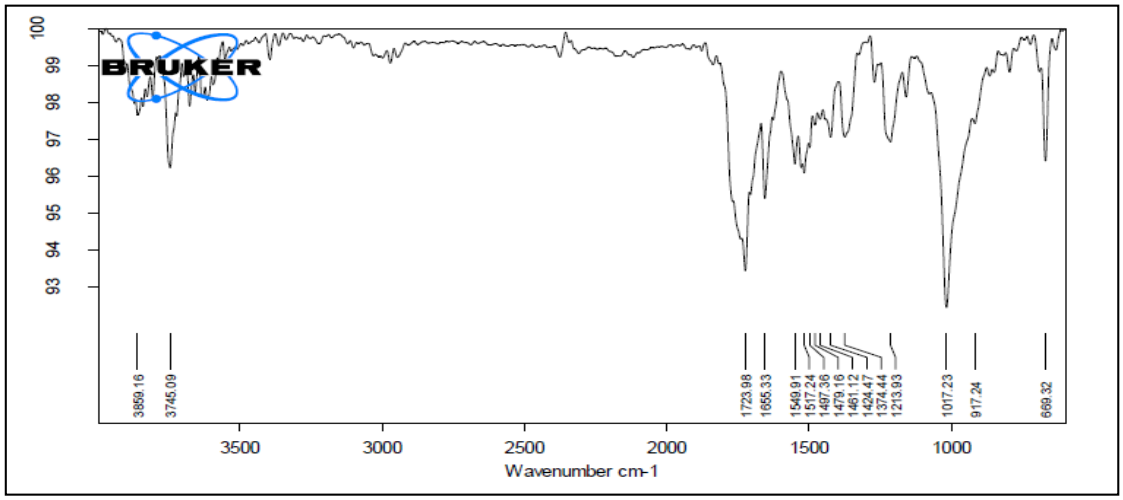

Fig 2: FTIR graph of optimized formulation

7.3 Determination of absorption maximum (λmax) of Eplerenone

Determination of Eplerenone λ-max was done for accurate quantitative assessment of drug dissolution rate.

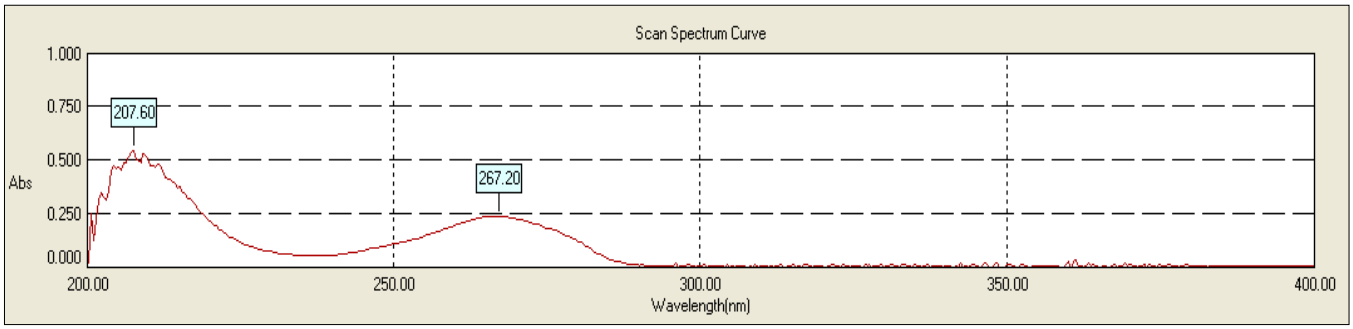

Fig 3: Absorption maximum (λ_{max}) of Eplerenone 267nm.

7.4 Standard calibration curve of Eplerenone

Eplerenone 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.

Table 2: Calibration curve of eplerenone in 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
5	0.118
10	0.241
15	0.362
20	0.479
25	0.602
30	0.712

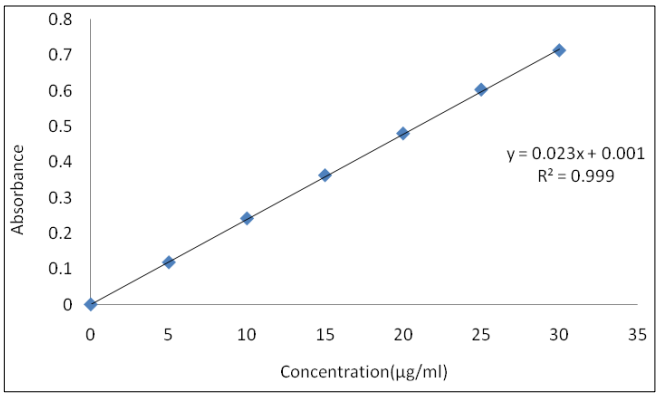

Fig 4: Calibration curve of Eplerenone in 0.1N HCl

Drug content

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

Table 3: Percentage Drug content of Eplerenone *in situ* 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

In-Vitro Gelation study

Gelling studies were carried out using 0.1N HCl and the obtained data were represented in Table 4. 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 calcium ions. 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. This is due to the internal inotropic Gelation effect of calcium on sodium alginate.

Table 4: *In-vitro* graded gel response data

Formulation Code	Graded Gel Response
F1	++
F2	++
F3	+++
F4	++
F5	++
F6	+++
F7	+
F8	++
F9	+++

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 5: Viscosity data

Formulation Code	Viscosity(cps)
F1	298
F2	316
F3	335
F4	349
F5	361
F6	392
F7	215
F8	268
F9	301

In vitro floating study

The formulated floating *in-situ* gelling system of Eplerenone 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 6: *In vitro* 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

In- vitro drug release study

The *in -vitro* release study of Eplerenone from all formulations in 0.1N HCl was conducted for a period of 12 hours. From the *in vitro* drug release studies of Eplerenone oral *in-situ* gels using different polymer ratios.

Among all 9 trails F1-F3 trails were formulated using Xanthan gum in three different ratios the drug release time was increased with increase in the polymer concentration. F1 formulation 97.42% of drug release at the end of 7 hours, while F2 formulation shows 98.21% of drug release at the end of 9hours, whereas F3 formulation shows 97.02% of drug release at the end of 11hours. Among all the three formulations can't sustained the drug release for 12hours. So further formulations were prepared using Guar gum.

Then F4-F6 trails were formulated using Guar gum in three different ratios, the drug release time was increased with increase in the polymer concentration. F4 formulation shows 97.5% of drug release at the end of 9hours, while F5 formulation shows 98.52% of drug release at the end of 11hours, whereas F6 formulation shows 97.08% of drug release at the end of 12 hours.

Then F7-F9 trails were formulated using Karaya gum in different ratios. F7 formulation shows 97.52% of drug release at the end of 6hours, while F8 formulation shows 98.41% of drug release at the end of 8hours, whereas F9 formulation shows 99.63% of drug release at the end of 10hours.

Among the all 9 formulations, based upon the *in-vitro* studies F6 formulation containing higher concentration of Guar gum chosen as optimized formulation, and has higher viscosity nature the formulation with higher concentration of Guar Gum maintains sustained drug release.

Table 7: *In vitro* drug release of Eplerenone floating *in-situ* gel

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.86	30.56	22.15	30.86	22.15	18.26	42.52	36.49	30.53
2	45.28	39.48	29.63	39.86	32.05	26.12	56.19	45.53	43.62
3	52.69	46.19	35.49	46.18	41.86	32.86	68.23	52.63	58.42
4	64.19	51.05	42.18	52.36	53.19	40.84	79.82	59.86	62.09
5	79.32	57.05	49.76	61.08	59.63	47.88	86.05	64.52	68.48
6	86.19	67.49	56.05	69.78	65.05	59.63	97.52	72.46	75.21
7	97.42	76.28	62.49	76.19	72.15	64.08		86.29	79.02
8		89.26	72.46	82.63	79.52	76.49		98.41	83.24
9		98.21	79.08	97.5	85.63	83.19			90.62
10			86.49		90.86	89.36			99.63
11			97.05		98.52	94.63			
12						97.08			

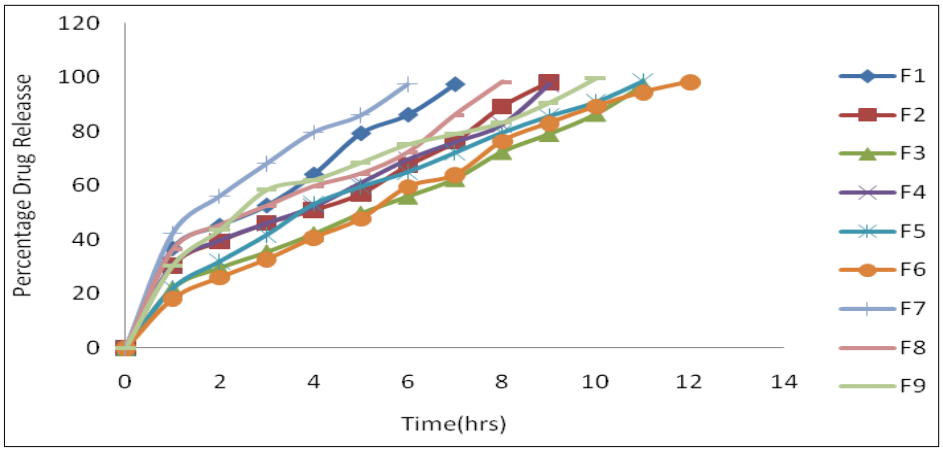

Fig 5: *In vitro* dissolution profile of F1-F9

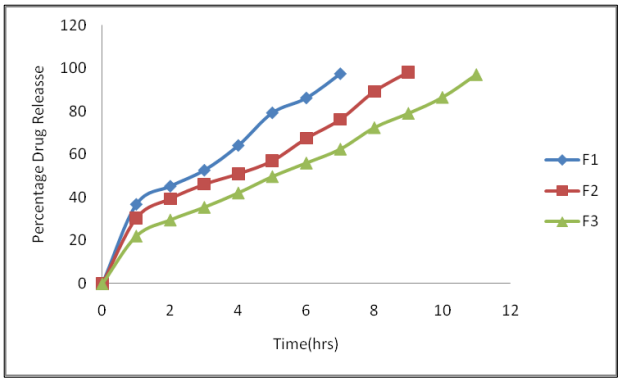

Fig 6: *In vitro* dissolution profile of F1-F3

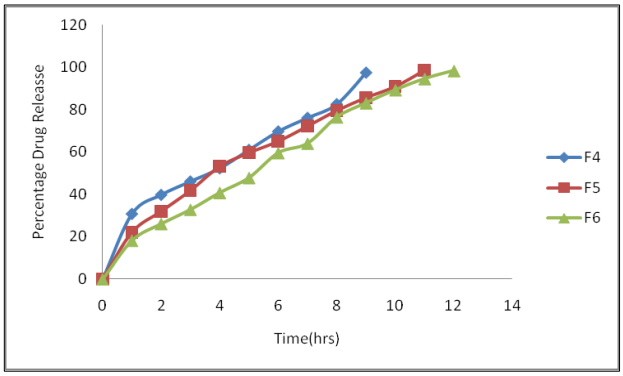

Fig 7: *In vitro* dissolution profile of F4-F6

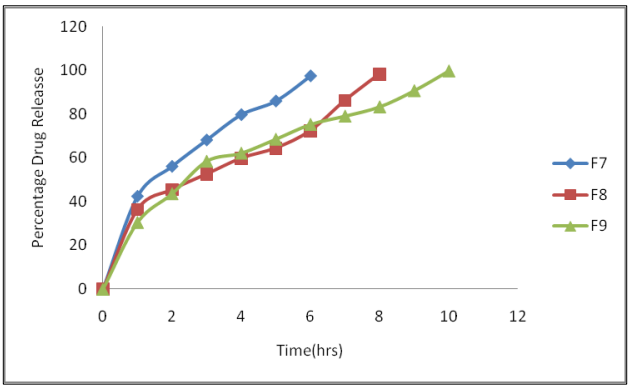

Fig 8: *In vitro* dissolution profile of F7-F9

Drug release kinetic studies

The *in-vitro* dissolution data for best formulation F6 were fitted in different kinetic models i.e., zero order, first order, Higuchi and Korsmeyer-Peppas equation. Optimized formulation F6 shows R^2 value 0.985. 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 behaviour or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The 'n' value is 1.204 for the optimised formulation (F6) i.e., n value indicates super case II transport mechanism.

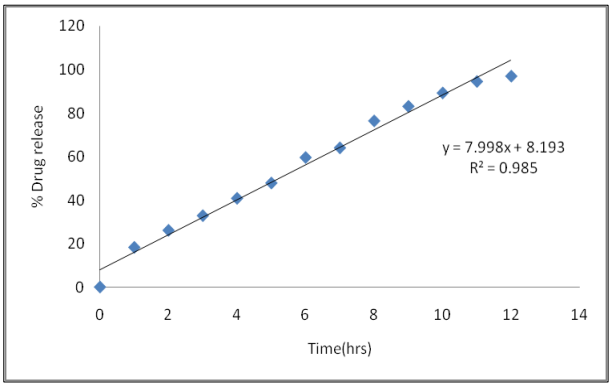

Fig 9: Zero order release graph for formulation F6

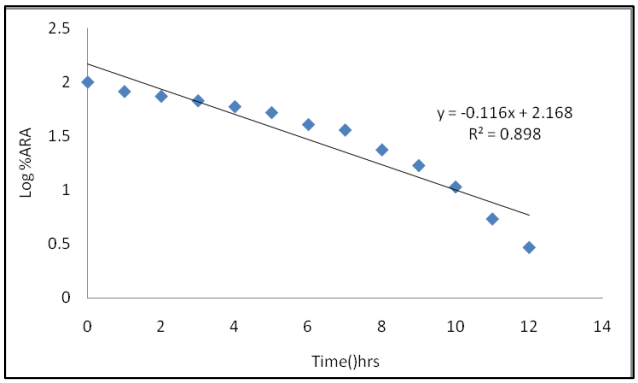

Fig 10: First order release graph for formulation F6

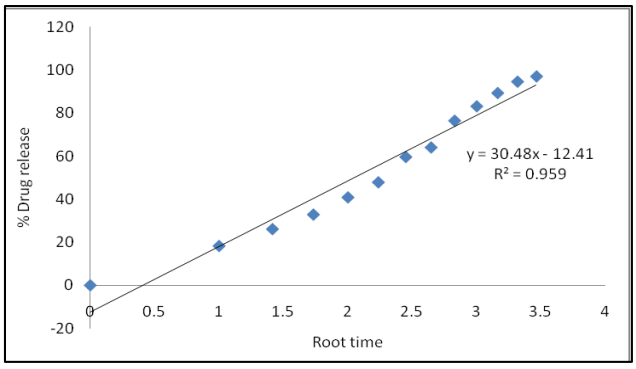

Fig 11: Higuchi release graph for formulation F6

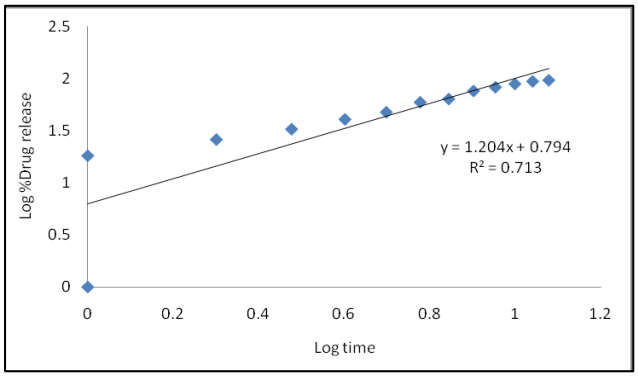

Fig 12: Peppas release graph for formulation F6

Table 8: Drug release kinetics data of Formulation F6

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer- Peppas (n)**
F6	0.985	0.898	0.959	0.713	1.204

Conclusion

From the above experimental results, it can be concluded that the release of eplerenone can be sustained by formulating it as *in-situ* gel. The results of study demonstrate that guar gum was suitable to develop sustained release oral *in-situ* gels.

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