International Journal of Indigenous Herbs and Drugs

Open Access

ISSN: 2456-7345

Formulation development and characterization of eplerenone insitu oral gels

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Article Info :

Article History

Received on: 28-04-2021

Revised on : 13-05-2021

Accepted on : 08-06-2021

Abstract

Gastro retentive drug delivery systems have been widely used to prolong the retention of dosage forms in the stomach. Among the various approaches, the floating in-situ gelling formulation offers sustained drug release as well as prolonged gastric retention, along with the added advantage of the liquid oral dosage form. The present study was an attempt to formulate and evaluate floating in situ gel of Eplerenone by using various polymers like Xanthan gum, Carbopol, HPMC K100M, and Karaya gum which undergoes pH dependent sol-gel transition at gastric pH, thereby prolonging the retention of the system in the 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 were subjected for compatibility study using FTIR studies, which revealed that there was no interaction between drugs and polymers. The evaluation was carried out for *invitro* parameters such as gelling nature, Total floating time, drug content, viscosity, & in vitro dissolution studies. Among all the formulations, the F12 formulation containing HPMC K100M was chosen as an optimized formulation that 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, Eplerenone, Sodium alginate, Calcium carbonate.

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Introduction

The development of in situ gelling systems has received considerable attention over the past few years. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of Temperature dependent, Ph dependent and action induced gelation. Compared to conventional controlled release

formulations, in situ forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort. 1-2 Insitugel forming drug delivery is a type of much adhesive drug delivery system. In contrastively strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of insitu gels. In situgel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic cross-linking³⁻⁵. So, insitu gels are administered by oral, ocular, rectal, vaginal injectable and intra-peritoneal route recent advances in insitu gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance [6].

Advantages of in-situ gels [6-7]

- Ease of administration
- To increase local bioavailability
- Reduced dose frequency
- Improved patient compliance
- Improved patient compliance
- Its production is less complex and so lowers the investment

Disadvantages [7]

- Not suitable for stomach irritating drugs
Ex: Aspirin and non-steroidal anti-inflammatory drugs Eplerenone 8, an aldosterone receptor antagonist similar to spironolactone, has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone. Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Fig o1:Chemical Structure of Eplerenone**Materials**

Eplerenone from BMR Chemicals, Hyderabad, Sodium alginate from Color cone Asia Ltd., Verna, Goa, Calcium carbonate, Sodium citrate, Ethyl cellulose MJ Biopharmaceuticals, Mumbai, HPMC K4M, Carbopol 934 from Otto Chemicals, Hyderabad Water Narmada chemicals

Methods**Preformulation studies [9-13]****Solubility studies**

Solubility of Eplerenone was determined in Methanol, Ethanol, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Eplerenone in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 244 nm.

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 color was recorded for initial evaluation and loaded into stability chambered at 40° c 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.

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 2ml of methanol then makeupto10ml with 6.8pH buffer so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 6.8pH buffer to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 6.8pH 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

10mg of Eplerenone was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with pH 1.2 Acidic buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with pH 1.2 Acidic buffer to get 2 to 12µg/ml of Eplerenone. The absorbance of the solution were measured against pH 1.2 Acidic buffer as blank at 244nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Method of Preparation of In-situ Gel

Floating *in situ* gel formulations of Eplerenone were prepared using compositions given in Table .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 [14-18]

Table 01: Formulation of Eplerenone Oral Insitu Gels

Ingre dient s (g)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 1 0	F 1 1	F 1 2
Epler enone	0 . 5	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4	0 . 4
Sodiu m algina te	1	1	1	1	1	1	1	1	1	1	1	1
Calciu m carbo nate	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5
Sodiu m citrat e	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5	0 . 5
Ethyl cellul ose	0 . 2 5	0 . 5	0 . 7 5	1	-	-	-	-	-	-	-	-
Carbo pol 934	-	-	-	-	0 . 2 5	0 . 5	0 . 7 5	1	-	-	-	-
HPMC K4M	-	-	-	-	-	-	-	-	0 . 2 5	0 . 5	0 . 7 5	1
Water (ml)	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0	1 0 0

Evaluation parameters of oral in-situ gels**Visual Appearance and Clarity**

Visual appearance and Clarity was done under fluorescent light against a white and black background for presence of any particulate matter.

pH Measurement

The pH of the prepared in-situ gel in a system after addition of all the ingredients was measured using pH meter.

Determination of drug content

Accurately 5 mL of formulation from different batches was measured and transferred to 100 mL volumetric flask. To this 50-70 mL of 0.1 N HCL was added and sonicated for 30 min. Volume was adjusted to 100 mL. Complete dispersion of contents was ensured visually and the dispersion was filtered using Whatman Filter Paper. From this solution, 1 mL of sample was withdrawn and diluted to 10 mL with 0.1 N HCL. Contents of Eplerenone was measured at maximum absorbance at 266 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 $37 \pm 0.5^\circ\text{C}$ and at 50 rpm using 900 mL of 0.1 N HCL (pH 1.2). In situ gel equivalent to 20 mg of Eplerenone was used for the test. Sample solution (5 mL) was withdrawn at predetermined time intervals, filtered through a 0.45 μm membrane filter, diluted and suitably analyzed by UV spectrophotometric LABINDIA 8000 at 266 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.

Release Kinetics [19-20]

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 insitu gels. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

Kinetic Studies: Mathematical 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.

Zero-order model

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

$$Q_t = Q_0 + K_0t$$

Where Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. To study the release

kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

Application: It is used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as tablets with low soluble drugs in coated forms, osmotic systems, etc.

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:

$$\log C = \log C_0 - kt/2.303$$

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

C_0 is the amount of drug dissolved at $t=0$ and

k is the first order rate constant.

A graph of log cumulative of % drug remaining vs time yields a straight line.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

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 geometries 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

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

Where, KH 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, first 60% drug release data were fitted in Korsmeyer-Peppas model,

$$M_t / M_\infty = K t^n$$

where M_t / M_∞ 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 02: 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 *in situ* 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

Saturation Solubility of Eplerenone

Solubility of Eplerenone was determined in 0.1 N HCL, 7.4 pH buffer, & 6.8 phosphate buffer and values obtained were noted in the table given below.

Table :3 Solubility studies of Eplerenone in various solvents

Solvents	Solubility($\mu\text{g/ml}$)
0.1 N HCL or 1.2pH Acidic buffer	0.559
6.8 pH buffer	0.262
7.4pH buffer	0.244

Fig :2 Solubility studies of Eplerenone

From the above solubility data we can say that Eplerenone has more solubility in 0.1N HCl or 1.2 pH Acidic buffer.

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 ascertain 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 03: FTIR graph of pure Eplerenone

Fig 04: FTIR graph of optimized formulation

Determination of absorption maximum (λ_{max}) of Eplerenone

Determination of Eplerenone λ_{max} was done for accurate quantitative assessment of drug dissolution rate.

Fig 05: Absorption maximum (λ_{max}) of Eplerenone 266 nm

Standard calibration curve of Eplerenone

Table 4: Calibration curve data Eplerenone in 0.1N HCl

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.138
10	0.264
15	0.426
20	0.551
25	0.691
30	0.816

Fig 06: Calibration curve of Eplerenone in 0.1N HCl
Eplerenone beer's range concentration was found to be in the range of 5-30 $\mu\text{g/ml}$ 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.

Drug content

Table 05: Percentage Drug content of Eplerenone in situ gels

Formulation code	Drug content (%)
F1	95.53
F2	96.76
F3	97.34
F4	95.85
F5	98.46

F6	99.45
F7	97.72
F8	100.73
F9	97.52
F10	98.45
F11	96.82
F12	98.48

Discussion

The drug content was found to being the range of 95.53-100.73% for all the formulations indicating uniform distribution of drug.

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 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 than those containing CaCO_3 . This is due to the internal ionotropic Gelation effect of calcium on sodium alginate.

Table 06: Invitro graded gel response data

Formulation Code	Graded Gel Response
F1	+
F2	++
F3	++
F4	+++
F5	++
F6	++
F7	++
F8	+++
F9	++
F10	++
F11	+++
F12	+++

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 < Ethyl cellulose < Carbopol < HPMC K100M. 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 07: Viscosity data of Oral Insitu Gels of Eplerenone

Formulation Code	Viscosity(cps)
F1	267
F2	287
F3	312
F4	245
F5	256
F6	274
F7	289
F8	377
F9	386
F10	394
F11	407
F12	422

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 08: Invitro floating Studies

Formulation code	Total floating Time (hrs)
F1	~8
F2	~9
F3	~11
F4	~11
F5	~8
F6	~10

F7	~12
F8	~12
F9	~9
F10	~11
F11	~12
F12	~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.

Table 09: In vitro drug release of Eplerenone floating insitu gel F1-F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	23.8 3	22.4 2	17.4 2	26.7 2	20.3 7	19.4 6
2	34.8 5	34.0 9	26.7 2	34.4 2	29.4 8	27.0 8
3	45.9 5	46.4 6	35.9 6	42.1 5	37.7 1	36.0 8
4	58.8 5	59.7 2	46.8 2	50.8 2	47.9 5	45.1 6
5	72.0 5	70.0 8	57.1 3	58.1 8	59.3 1	54.0 5
6	85.9 2	82.2 3	68.1 6	66.5 6	71.3 1	65.8 2
7		96.1 6	77.8 2	74.3 2	83.6 3	76.3 8
8			88.1 3	82.7 3	95.6 2	87.0 7
9			97.0 6	90.4 8		96.1 3
10				98.3 5		
11						
12						

Table 10: In vitro drug release of Eplerenone floating insitu gel F7-F12

Time (hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	16.1 8	13.4 5	20.0 8	18.0 5	14.4 6	10.0 5
2	23.7 5	21.5 3	30.4 6	27.4 3	25.2 8	16.5 9
3	34.0 9	27.4 1	41.0 6	36.9 8	33.7 2	24.4 9

4	44.1 6	34.0 8	50.0 8	46.6 5	41.1 8	31.1 5
5	53.0 8	40.1 6	63.7 9	56.5 8	50.0 2	37.7 5
6	61.6 3	48.0 9	77.8 6	68.1 3	57.9 5	46.3 6
7	69.4 2	55.1 3	95.1 9	81.1 3	65.1 3	56.1 2
8	75.9 8	61.3 1		95.6 7	74.0 5	67.4 3
9	83.5 5	69.0 6			85.4 6	78.1 8
10	90.5 5	78.4 3			96.4 2	88.0 2
11	97.7 4	88.1 4				98.0 6
12		99.5 4

Fig 07: In vitro dissolution profile of F1-F12

Fig 08: In vitro dissolution profile of F1-F4

Fig 09: In vitro dissolution profile of F5-F8

Fig 10: Invitro dissolution profile of F9-F12

From the in vitro drug release studies of Eplerenone oral insitu gels using different polymer ratios. Among the all 12 trails F1-F4 trails were formulated using Ethyl cellulose in three different ratios the drug release time was increased with increase in the polymer concentration. F1 formulation 85.92% of drug release at the end of 6hours, while F2 formulation shows 96.16% of drug release at the end of 7hours, while F3 formulation shows 97.06% of drug release at the end of 9hours, whereas F4 formulation shows 98.73% of drug release at the end of 10hours. Among all the three formulations cant sustained the drug release for 12hours. So further formulations were prepared using Carbopol. Then F5-F8 trails were formulated using Carbopol in different ratios. F5 formulation shows 95.62% of drug release at the end of 8hours, while F6 formulation shows 96.13% of drug release at the end of 9hours, while F7 formulation shows 97.74% of drug release at the end of 11hours, whereas F8 formulation shows 99.54% of drug release at the end of 12hours. Then F9-F12 trails were formulated using HPMC K4M in different ratios. F9 formulation shows 95.19% of drug release at the end of 7hours, while F10 formulation shows 95.67% of drug release at the end of 8hours, whereas F11 formulation shows 96.42% of drug release at the end of 10hours, whereas F12 formulation shows 98.06% of drug release at the end of 11hours. Among the all 12 formulations, based upon the invitro studies F8 formulation containing higher concentration of Carbopol choosen as optimized formulation, and has higher viscosity nature the formulation with higher concentration of Carbopol maintains sustained drug release. So the drug release kinetics were performed for the F8 formulation.

Drug release kinetic studies

Zero order release kinetics:F8

Fig 11: Zero order release graph for F8

First order release kinetics: F8

Fig 12: First order release graph for F8

Higuchi release plot

Fig 13: Higuchi release graph for F8

Peppas release plot

Fig 14: Peppas release graph for F8

Table 11: Drug Release Kinetics of Eplerenone Oral Insitu Gels

Formula tion	R ² values				n values
	Zer o ord er	Fir st ord er	Higu chi	Korsm eyer - Peppas	Korsme yer- Peppas (n)
F12	0.993	0.598	0.920	0.764	1.123

The invitro dissolution data for best formulation F8 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsmeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.993. 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 1.123 for 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.11

Summary and conclusion

Eplerenone oral in-situ gelling systems were prepared by using polymers like HPMC K4M, Carbopol, Ethyl cellulose, Sodium citrate, Calcium carbonate and Sodium alginate. Total of twelve (F1 to F12) formulations were prepared and F12 containing HPMCK4M was found to be the best formulation. 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 F12 formulation containing HPMCK4M shows drug release of 97.34% by the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model ($R^2=0.920$) and showed zero order ($R^2=0.993$) drug release with super case II transport mechanism. From the above experimental results it can be concluded that, Eplerenone 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 HPMC K4M was suitable to develop sustained release oral insitu gels.

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