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Formulation Development and Characterization of Eplerenone Insitu Oralgels

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ABSTRACT

Gastro retentive drug delivery systems have been widely used to prolong retention of dosage forms in 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 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 dependant 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 *invitro* parameters such as gelling nature,Total floating time, drug content, viscosity, & in vitro dissolution studies. Among all the formulations, F12 formulation containing HPMC K100M was choosen as optimized formulation which shows maximum drug release by the end of 12hrs and has excellent floating characteristics and gastric retention. From kineticstudies the optimized formulation shows zero order release with super case II transport mechanism.

KEYWORDS: Eplerenone Sodium alginate, Calcium carbonate, Sodium citrate, Ethyl cellulose, HPMC K4M, Carbopol 934.

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 cation 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.[1-3] In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very 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 in situ gels. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic cross- linking[4-7]. So, in situ gels are administered by oral, ocular, rectal, vaginal injectable and intra-peritoneal route Recent advances in in situ 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.[8-14]

MATERIALS AND METHODS

Eplerenone were obtained from BMR Chemicals, Hyderabad. Sodium alginate, Calcium carbonate,Sodium citrate, Ethyl cellulose, HPMC K4M, Carbopol 934 were obtained from Otto Chemicals, Hyderabad.

Method of Preparation of *In-situ* Gel:

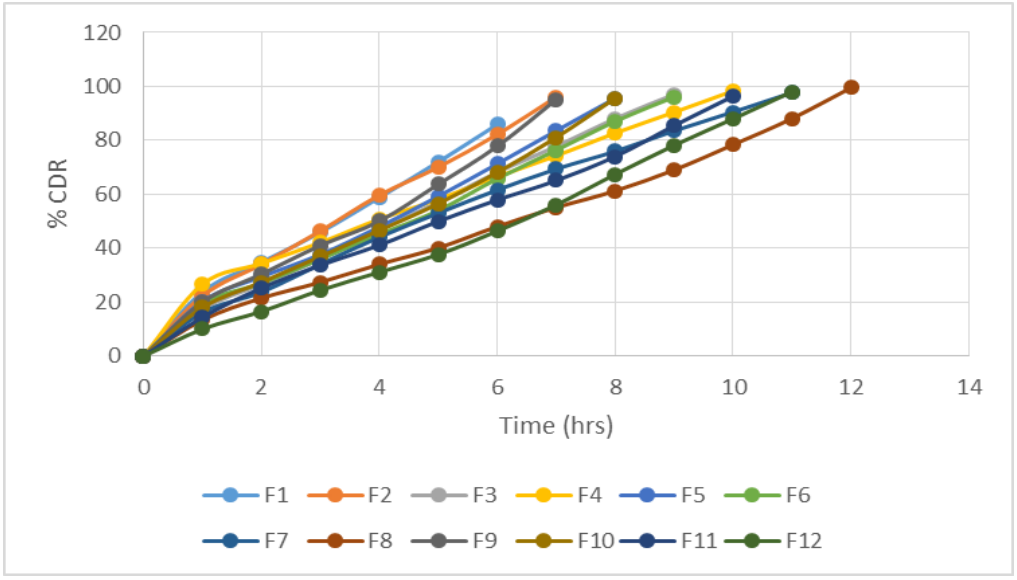
Floating *in situ* gel formulations of Eplerenone were prepared using compositions given in Table .Take 100ml beaker, in that beaker take sodium alginate and add with polymer, then mix with 60ml distilled water, now heat the mixture at 60°C till solution occurs using a heating magnetic stirrer .Take 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.

Formulation of Eplerenone Oral Insitu Gels

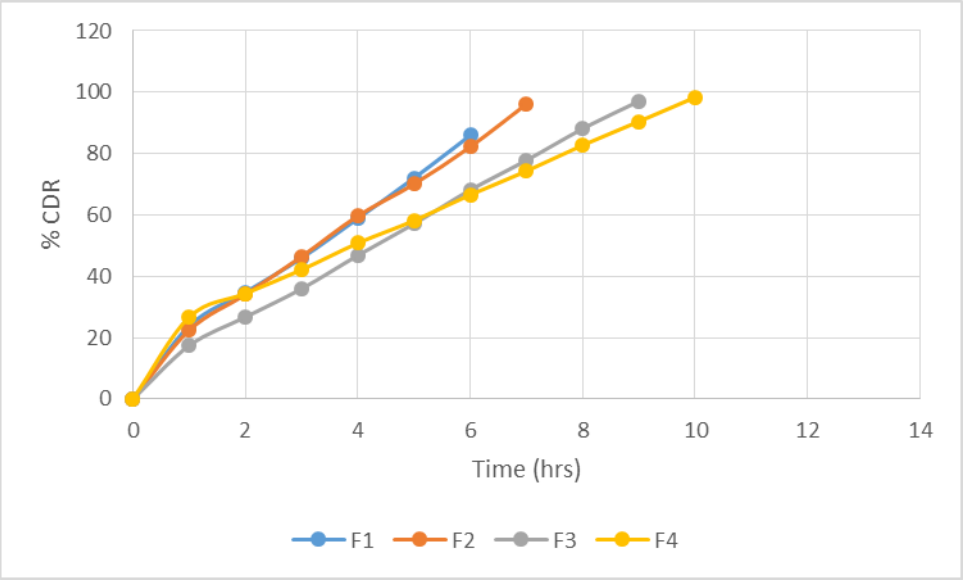
Ingredients (g)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Eplerenone	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium alginate	1	1	1	1	1	1	1	1	1	1	1	1
Calcium carbonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose	0.25	0.5	0.75	1	--	--	--	--	--	--	--	--
Carbopol 934	--	--	--	--	0.25	0.5	0.75	1	--	--	--	--
HPMC K4M	--	--	--	--	--	--	--	--	0.25	0.5	0.75	1
Water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

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 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.



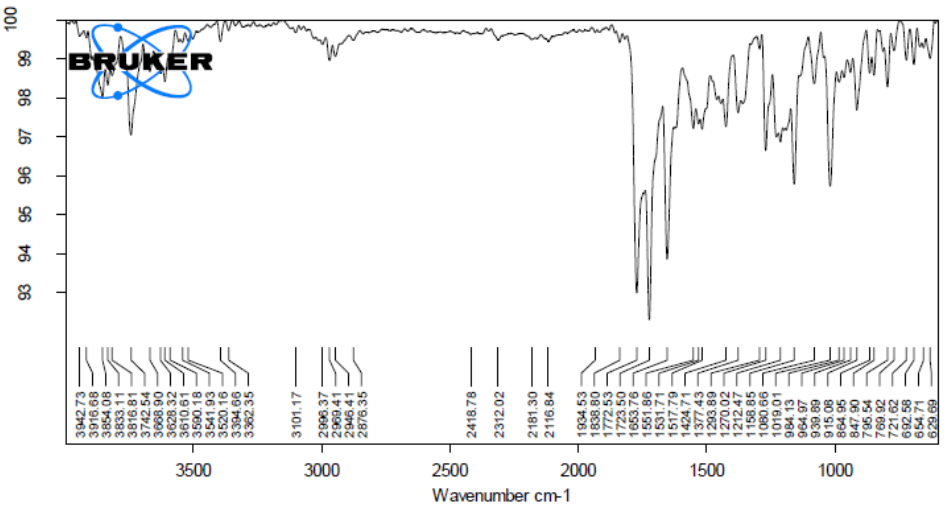
Invitro dissolution profile of F1-F12



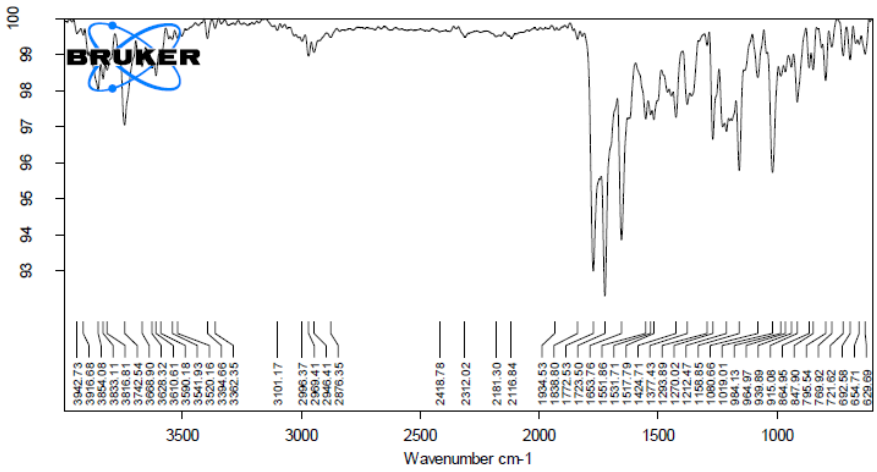
Invitro dissolution profile of F1-F4

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.



FTIR graph of pure Eplerenone



FTIR graph of optimized formulation

Determination of absorption maximum (λmax) of Eplerenone:

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

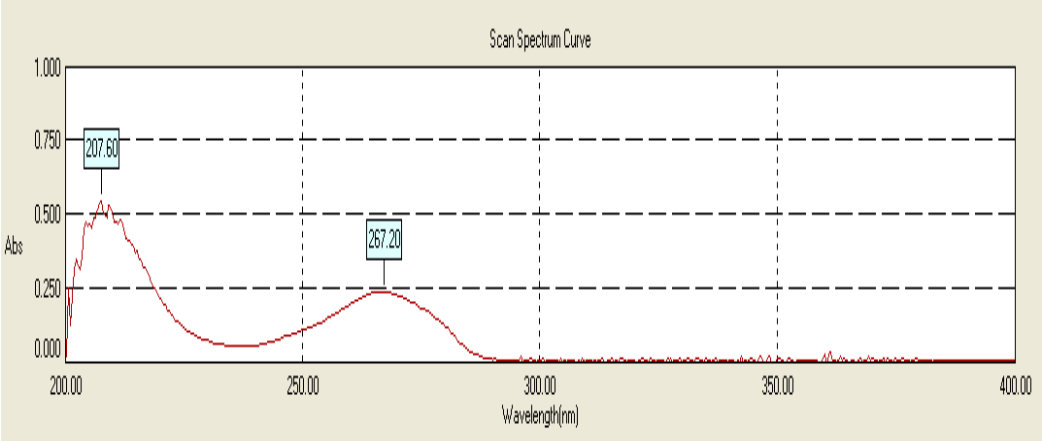
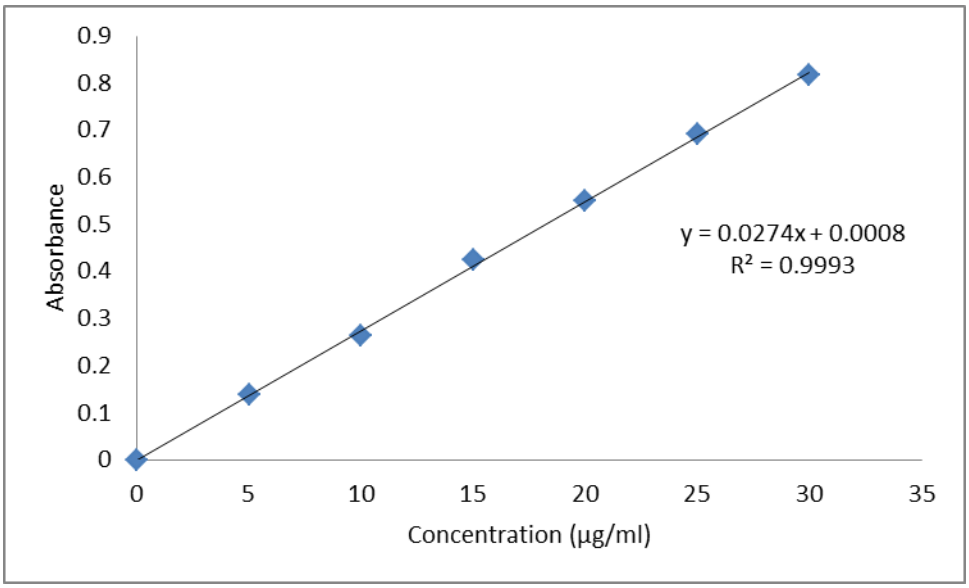


Fig : Absorption maximum (λ_{max}) of Eplerenone 266nm.

Standard calibration curve of Eplerenone:

Calibration curve data Eplerenone in 0.1N HCl

Concentration (µg/ml)	**Absorbance**
0	0
5	0.138
10	0.264
15	0.426
20	0.551
25	0.691
30	0.816



Calibration curve of Eplerenone in 0.1N HCl

Discussion: 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.

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.

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 : 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.

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

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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