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FORMULATION AND EVALUATION OF EPLERENONE HYDROGEL BEADS

Umasankar K, Saranya M*, Jayachandra Reddy P

Department of Pharmaceutics,
Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati - 517506, Andhra Pradesh, India.

ABSTRACT

The main aim of the present work is to formulated and evaluate hydrogel beads of eplerenone by ionic gelation method using HPMC K100M, HPMC K200M, Xanthan gum and karaya gum. Formulated beads were evaluated for preformulation studies. The FTIR Spectra revealed that, there was no interaction between Eplerenone and polymers. Surface smoothness of the Eplerenone beads was confirmed by SEM. As the ratio of polymer was increased, the mean particle size of Eplerenone floating beads was decreased. Eplerenone floating beads with normal frequency distribution were obtained. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The in vitro performance of Eplerenone Hydrogel beads showed prolonged and controlled release of drug which follows zero order release with supercase II transport mechanism.

Key Words:- Eplerenone, FTIR, Xanthan gum, Karaya gum, HPMC K100M.

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Corresponding Author

Saranya M
Department of Pharmaceutics, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati - 517506, Andhra Pradesh, India.

Email:- saranya0037@gmail.com

INTRODUCTION

There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs (Fursule RA *et al*., 2009).

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm) (Garg R *et al*., 2008). Microspheres are sometimes referred to as microparticles (Gattani YS *et al*., 2009). Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid (Jain AK *et al*., 2009). The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract (Xu WL *et al*., 1991).

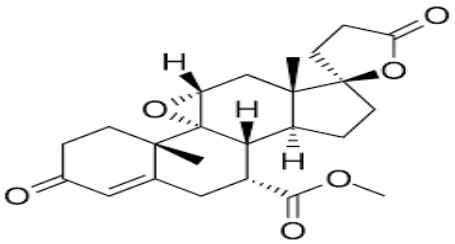
Drug Profile

Eplerenone

Synonyms: Eplerenona; Eplerenone; Epoxymexrenone

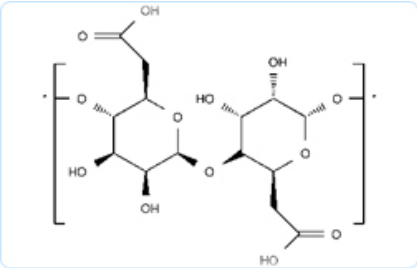
Categories: Agents causing hyperkalemia; Antihypertensive Agents; Cardiovascular Agents; Diuretics; Fused-Ring Compounds; Hormone

Antagonists; Natriuretic Agents; Potassium-Sparing Diuretics; Pregnanes
CAS number: 107724-20-9
Structure



Weight
Average: 414.4914
Monoisotopic: 414.204238692
Chemical Formula: $C_{24}H_{30}O_6$
IUPAC Name:
Methyl (1'R,2R,2'S,9'R,10'R,11'S,15'S,17'R)-2',15'-dimethyl-5,5'-dioxo-18'-oxaspiro[oxolane-2,14'-pentacyclo[8.8.0.0^{1},^{17}.0^{2},^{7}.0^{11},^{15}]octadecan]-6'-ene-9'-carboxylate
Pharmacodynamics
Eplerenone, 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.
Mechanism of action
Eplerenone binds to the mineralocorticoid receptor and thereby blocks the binding of aldosterone (component of the renin-angiotensin-aldosterone-system, or RAAS) (Yeole PG *et al*., 2005). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium (Yuveraj Singh T *et al*., 2007).
Protein binding: 50%
Metabolism: Eplerenone is metabolized primarily by CYP3A4, however, no active metabolites have been identified in human plasma.
Half life: 4-6 hours

Polymer Profiles
Sodium Alginate
Structure



Nonproprietary Names: BP: Sodium Alginate PhEur: Sodium Alginate USP-NF: Sodium Alginate
Synonyms: Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol;Keltone; natrii alginas; Protanal; sodium polymannuronate.
Chemical Name and CAS Registry Number - Sodium alginate [9005-38-3]
Empirical Formula: Sodium alginate consists chiefly of the sodium salt of alginic acid,which is a mixture of polyuronic acids composed of residues of Dmannuronic acid and L-guluronic acid.
Functional Category: Stabilizing agent; Suspending agent; Tablet and capsule disintegrant; Tablet binder; Viscosity increasing agent.of sodium chloride is present.

Applications in Pharmaceutical Formulation
Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.

MATERIALS AND METHODS
Preformulation studies
Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

Determination of Melting Point
Melting point of Eplerenone was determined by capillary method. Fine powder of Eplerenone was filled in glass capillary tube (previously sealed at one end). The capillary tube was tied to thermo meter and the thermometer was placed in the Thais tube and this tube was placed on fire. The powder at what temperature it melted was noticed.

Solubility
Solubility of Eplerenone was determined in 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 243 nm.

Determination of λ_{max}
A solution of Eplerenone containing the concentration 25 µg/ ml was prepared in 6.8pH buffer and UV spectrum was taken using Shimadzu (UV-2550) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Calibration Curve of Eplerenone in 0.1NHCL

10mg of Eplerenone was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1 N HCL to get 5 to 30µg/ml of. The absorbance of the solution was measured against 0.1 N HCL as blank at 243nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Calibration Curve of Eplerenone in 6.8pH phosphate buffer

10mg of Eplerenone was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 6.8pH phosphate buffer to get 5 to 30µg/ml of. The absorbance of the solution was measured against 6.8pH phosphate buffer as blank at 243nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Drug polymer interaction (FTIR) study

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2 mg of Eplerenone alone, mixture of drug and polymer, beads were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 500–4000 cm-1 was recorded taking air as the reference and compared to study any interference.

Preparation of Eplerenone Hydro gel beads
Ionotropic Gelation method

Accurate quantity of polymer was dissolved in 25ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution and stirred until a homogenous mixture was obtained. The mixture was extruded through a 23G syringe needle into calcium chloride solution (2% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

Evaluation of Eplerenone Hydrogel Beads
Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry Eplerenone gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Eplerenone hydrogel beads were taken by random scanning of the stub.

Percentage yield

Percentage practical yield of Eplerenone hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Eplerenone beads recovered from each batch in relation to the sum of starting material.
The percentage yield of Eplerenone beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content

To determine the drug content and encapsulation efficiency of the beads, 10 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent. The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent, and drug content assayed using a UV-visible spectrophotometer at λmax of 243 nm. The drug content of each formulation was recorded as mg / 10 mg of gel beads.

Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation.

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

***In-vitro* dissolution studies**
Procedure for In-vitro dissolution study

The release rate of Eplerenone Hydrogel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, for 2hours and at 6.8pH buffer for 10hours, iat 37 ±0.5°C at 50 rpm. Eplerenone hydrogel beads equivalent to 25 mg of Eplerenone was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples

were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 243nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

Table 1. Formulation design for Eplerenone hydrogel beads using different ratios of drug and polymers

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Eplerenone	200	200	200	200	200	200	200	200	200	200	200	200
Sodium Alginate	100	200	300	100	200	300	100	200	300	100	200	300
HPMC K100M	100	200	300	-	-	-	-	-	-	-	-	-
HPMC K200M	-	-	-	100	200	300	-	-	-	-	-	-
Karaya gum	-	-	-	-	-	-	100	200	300	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	-	100	200	300
Calcium chloride(%)	2	2	2	2	2	2	2	2	2	2	2	2

RESULTS AND DISCUSSION

Table 2. Solubility study

Solvent	Solubility (mg/ml)
0.1N HCl	25.26
6.8pH buffer	16.09
7.4pH buffer	12.64
Water	15.75

Table 3. Standard calibration data of Eplerenone in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.172
10	0.319
15	0.482
20	0.649
25	0.802
30	0.967

Table 4. Standard calibration data of Eplerenone in 6.8pH buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.126
10	0.279
15	0.402
20	0.529
25	0.649
30	0.792

Table 5. Drug Content and Percentage yield of Eplerenone Hydrogel beads

Formulation Code	Percentage Yield	Drug content (%)
F1	82.64	98.58
F2	83.49	97.50

F3	92.75	96.48
F4	86.34	99.08
F5	95.62	95.68
F6	96.05	97.51
F7	79.08	99.48
F8	86.28	96.28
F9	92.64	95.63
F10	86.29	95.07
F11	89.41	96.84
F12	96.37	99.65

Table 6. *In vitro* release data of Hydrogel beads of Eplerenone (F1-F6)

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	32.64	23.84	16.85	23.85	19.85	10.52
2	49.65	45.26	36.51	29.08	26.85	23.64
3	55.08	50.46	42.68	36.49	30.64	29.75
4	59.79	56.89	51.08	42.08	39.75	36.18
5	65.74	69.72	59.76	53.94	45.15	45.80
6	72.94	76.49	65.79	62.97	51.49	54.10
7	86.34	80.67	71.84	69.08	64.19	62.41
8	99.08	89.46	79.46	76.49	71.95	70.72
9		97.65	86.49	89.35	79.46	79.03
10			90.36	95.97	86.09	87.34
11			98.63		92.68	95.65
12						98.05

Table 7. *In vitro* release data of Hydrogel beads of Eplerenone (F7-F12)

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	26.34	19.84	12.45	29.45	27.13	25.63
2	39.84	24.83	20.85	35.09	32.46	28.49
3	47.28	37.46	33.46	42.76	43.16	31.74
4	59.61	46.19	40.18	48.16	50.94	34.08
5	65.34	50.87	49.67	52.04	66.38	39.46
6	74.31	59.38	59.87	63.18	72.49	46.18
7	85.04	65.49	65.49	79.43	85.42	62.48
8	98.75	70.58	72.19	96.48	92.13	76.86
9		86.49	80.64		96.85	87.08
10		96.15	89.46			98.99
11			96.08			
12						

Table 8. Drug Release Kinetics

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	**r^2**	**r^2**	**r^2**	**r^2**	**n**
F6	0.995	0.839	0.943	0.795	1.304

Fig. 1. λmax of Eplerenone in 0.1N HCL

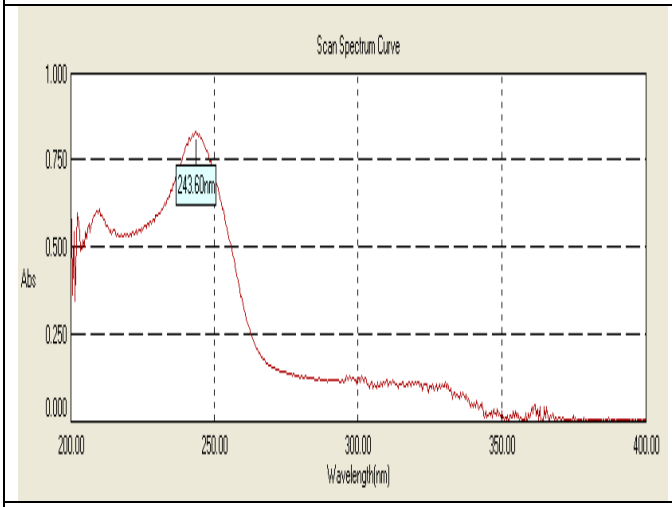


Fig. 2. Standard calibration curve of Eplerenone in 0.1N HCL

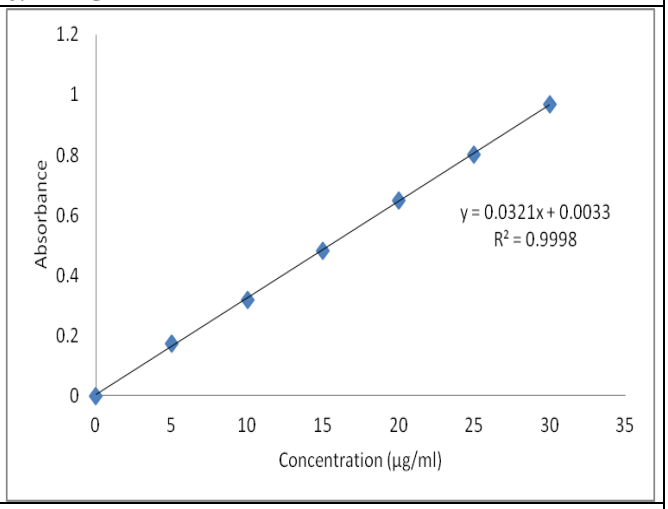


Fig. 3. Standard calibration curve of Eplerenone in 6.8pH buffer

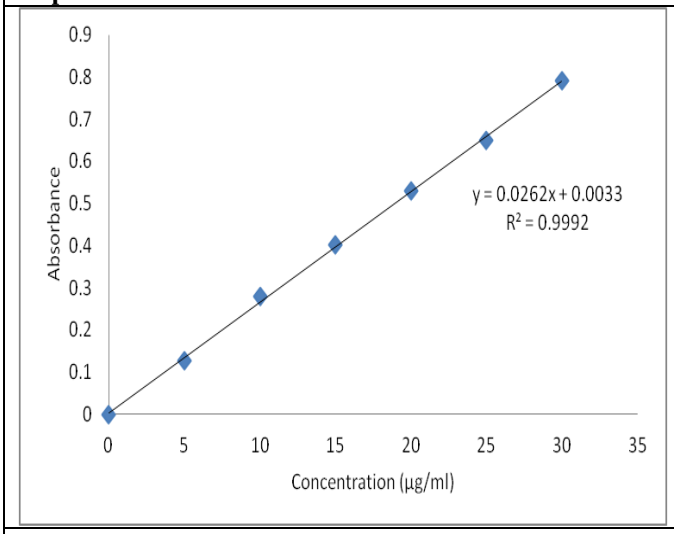


Fig. 4. SEM photographs of Hydro gel beads

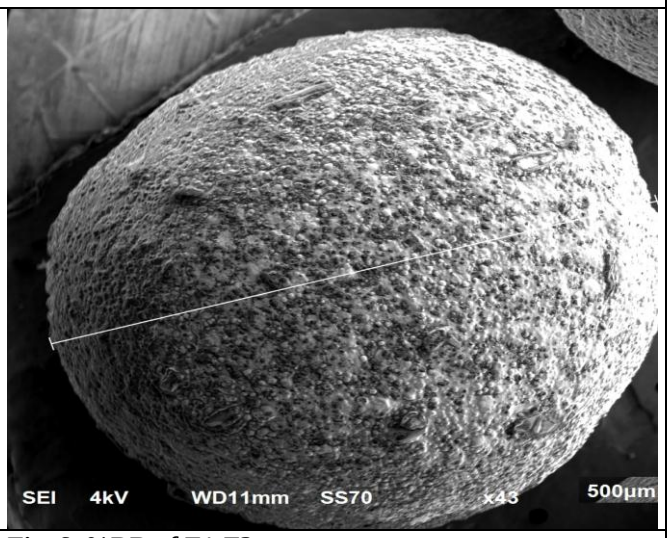


Fig. 5. %DR of F1-F9

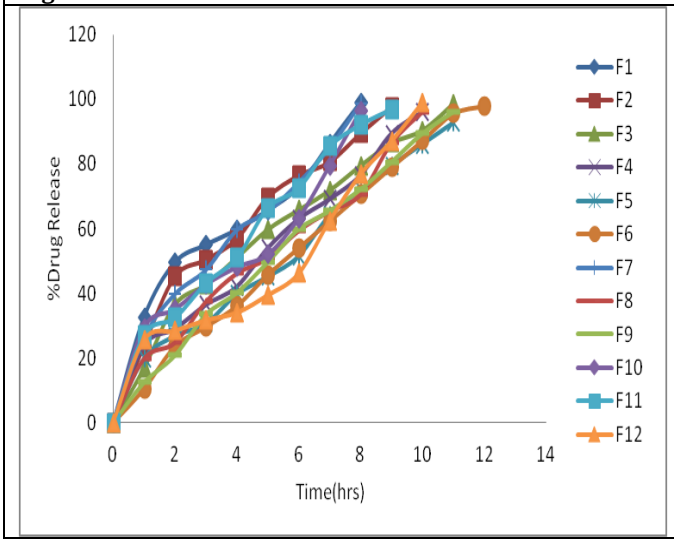


Fig. 6. %DR of F1-F3

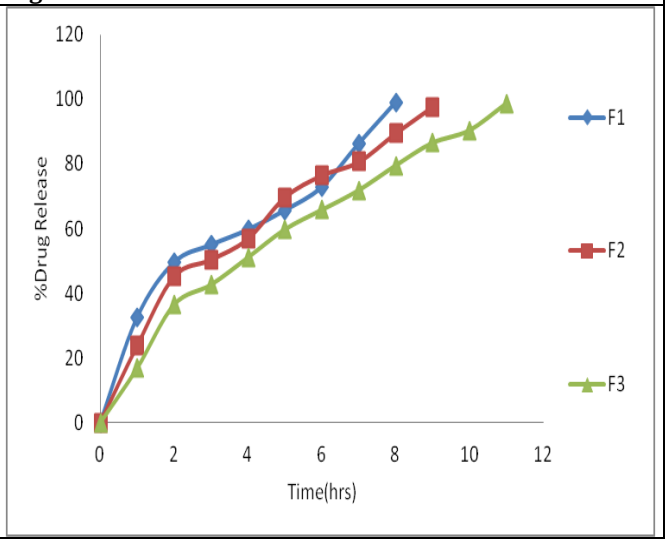


Fig. 7. Higuchi plot of F6 formulation

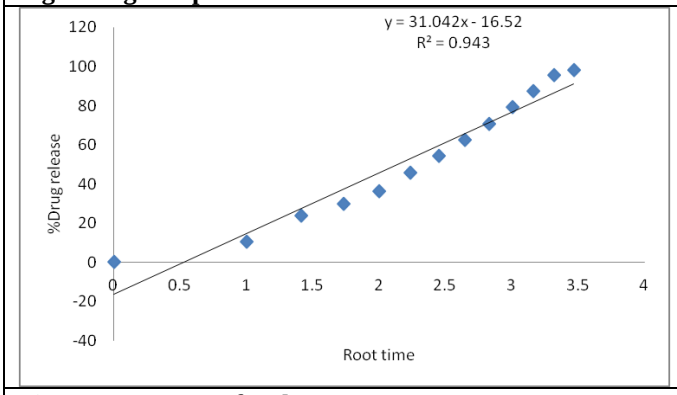


Fig. 8. Peppas plot of F6 formulation

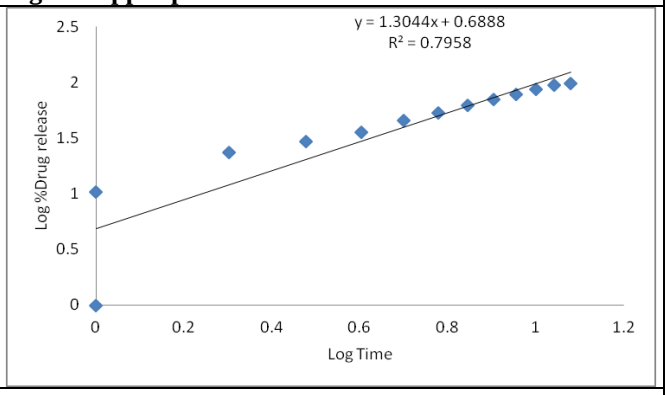


Fig. 9. IR spectra of Eplerenone

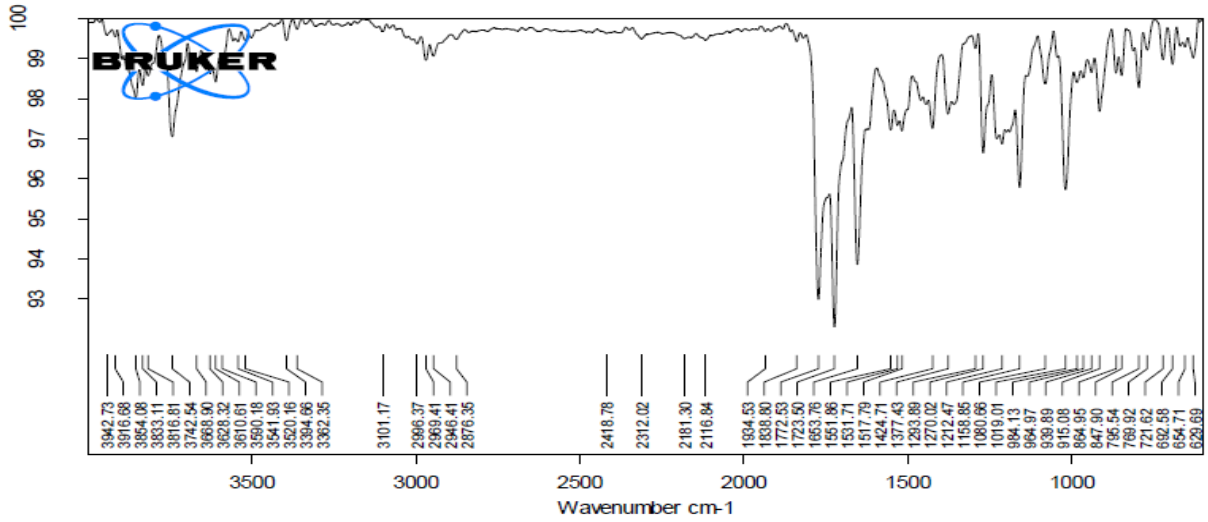
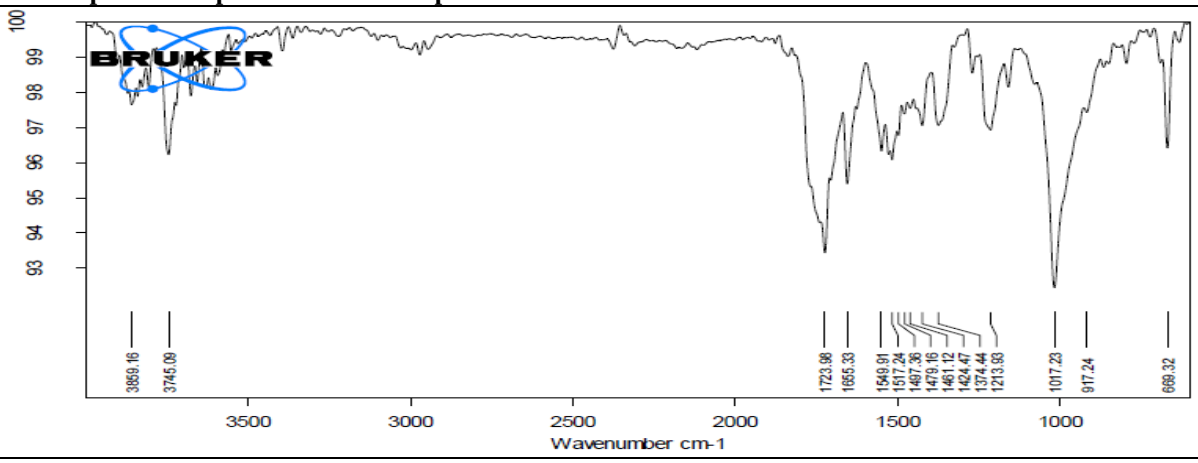


Fig. 10. IR spectra of Eplerenone and Excipients



Solubility study

From the solubility studies it was observed that Eplerenone was found to be more soluble in 0.1N HCL.

Evaluation of Eplerenone Hydrogel Beads

Drug polymer interaction (FTIR) study

From the spectra of Eplerenone, physical mixture of Eplerenone and polymer, Eplerenone and blank beads, it was observed that all characteristic peaks of Eplerenone were present in the combination spectrum, thus indicating compatibility of the Drug and polymer.

FTIR Spectra were obtained for Eplerenone, physical mixture, Eplerenone and polymers. The

characteristic peaks of the Eplerenone were compared with the peaks obtained for physical mixture of Eplerenone and polymer. From the obtained spectra it appeared that there were no interaction between Eplerenone and polymers.

Surface morphology - Scanning Electron Microscopy (SEM)

The surface morphology of the Eplerenone beads was studied by SEM. SEM photographs of the optimized formulation were shown in the Fig. 4. Surface smoothness was observed with HPMC K200M incorporated Eplerenone beads.

***In vitro* dissolution studies**

The *in vitro* performance of Eplerenone hydrogel beads showed prolonged and controlled release of Eplerenone. The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. As the polymer concentration was increased, the drug release from the hydrogel beads was found to decrease. Compared to xanthan gum, HPMC K100M and karaya gum, HPMC K200M retarded drug release more effectively, hydrogel beads had an optimum release at the end of 12th hour. Based upon our aim and Objective the main aim was to controlled the drug delivery by hydrogel beads, the maximum drug was controlled in HPMC K200M formulations than the other polymers. So Kinetic studies were measured for F6 formulation.

Drug Release Kinetics

From the drug release kinetics of the Eplerenone hydrogel beads it was concluded that the formulation F6 follows Zero order release with super case II transport mechanism.

CONCLUSION

The concept of formulating hydrogel beads containing Eplerenone offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, hydrogel beads of Eplerenone were prepared successfully by ionotropic gelation method using different polymers. From the above experimental results it can be concluded that: Preformulation studies like solubility and UV analysis complied with standards. The FTIR Spectra revealed that, there was no interaction between Eplerenone and polymers. Surface smoothness of the Eplerenone beads was confirmed by SEM. As the ratio of polymer was increased, the mean particle size of Eplerenone floating beads was decreased. Eplerenone floating beads with normal frequency distribution were obtained. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The *in vitro* performance of Eplerenone Hydrogel beads showed prolonged and controlled release of drug. The invitro dissolution data for best formulation F6 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F6 shows R^2 value 0.995. 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, The 'n' value is 1.304 for the optimised formulation (F6) i.e., n value was >0.89 this indicates Super case II transport.

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