Research Article

Formulation and Evaluation of Eplerenone Matrix Tablets using Aloe Vera, Guar Gum and Povidone K-30.

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Abstract

Purpose: In the existing work different sustained release matrix tablets of eplerenone were prepared with dried mucilage of *Aloe vera*, guar gum and povidone K30 by using different binder: tablet weight ratios viz. 1:20, 2:20, 3:20, 4:20 and 5:20. **Method:** During this process *Aloe vera* leaves are procured, extracted, dried and characterized to obtain *Aloe vera* mucilage powder. Pre-formulation studies were performed and studied for the functional groups and also compatibility studies were conducted. The formulations that were prepared using *Aloe vera* were named as EPA, for Guar gum as EPG, for Povidone K30 as EPP and finally combination of *Aloe vera* and Povidone K30 was named as EPAP. **Results:** From the graphs, kinetic evaluation was done and observed that the drug release is governed by diffusion mechanism and this is confirmed by *r* values. The regression coefficient values, clearly indicates that the drug release is governed by zero order and almost all formulations showing Fickian release. Among all the formulations that were prepared EPAP-5 is selected as best. The best formulation is compared with the marketed formulation. **Conclusion:** *Aloe vera* gel dried powder is a suitable matrix agent in formulating sustained release tablets of eplerenone. It may be useful in similar preparations of other drugs.

Key words: Eplerenone, Matrix tablets, *Aloe vera*, Guar gum, Povidone K-30.

Introduction

Among the entire delivery systems oral route is highly preferred because of its high comfort zone that cannot be produced by other routes. In order to release the drug at specific location different types of polymers are used and they also help to show prolonged action. Many advanced technologies are available and these are making the delivery systems more suitable and advantageous when compared to the past. Controlled release oral drug delivery

system is one among the advanced technologies that is most widely preferred. (1)

Eplerenone is a steroidal anti mineralocorticoid of the spiro lactone group that is used as an adjunct in the management of chronic heart failure. The recommended starting dose of eplerenone for the treatment of essential hypertension is 50 mg once daily titrated to a maximum of 50 mg twice daily.

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For the treatment of heart failure, the recommended starting dose is 25 mg once daily, titrated over 4 weeks if tolerated to the target dose of 50 mg once daily. No adjustment is necessary for patients with mild to moderate hepatic impairment or for the elderly. The maximum effective dose should be limited to 100 mg daily to avoid the increased risk of hyperkalemia with higher doses. The elimination half-life is 4 to 6 hours. Absolute bioavailability 69% (100-mg oral tablet). Peak plasma concentrations usually attained within 1.5–2 hours. Hence in the present work in order to decrease the dose and to make available the drug for prolonged period matrix tablets of eplerenone are formulated.

In the present investigation various matrix tablets were prepared by wet granulation using *Aloe barbadensis* Miller leaf mucilage dried powder, Guar gum and Povidone K-30 as polymers in different proportions. The prepared tablets are compared with the marketed product. (2)

Methods and Results

Materials

Eplerenone was procured from Dr. Reddy's Labs, Hyderabad, India, EPTUS tablets 50 mg, Glenmark pharmaceuticals Ltd., Mumbai, India, Batch no: 22110008 as marketed formulation, Guar gum, Povidone K 30, Microcrystalline cellulose, Magnesium stearate, Span 80, Glycerin and Propylene Glycol were procured from S.D. Fine Chemicals Ltd., Mumbai, India. Acetone and ethanol were procured from Ranbaxy Fine Chemicals Ltd., Delhi, India.

Aloe barbadensis Miller

Aloe vera is a stemless or very short-stemmed plant growing up to 60–100 cm height. The leaves are thick and fleshy, green to grey-green, with some varieties showing white flecks on their upper and lower stem surfaces consists of polycyclic aromatic hydrocarbons. It belongs to the Kingdom Plantae and Family Asphodelaceae. (3)

Equipment

Tablet compression machine, 10 station made by Karnavathi Engineering Ltd., Gujarat, India. Electronic balance made by Shimadzu, North America, pH meter, Model no.361 made by Systronics, Gujarat, India, Bulk density apparatus made by Electrolab, Mumbai, India, UV visible spectrophotometer made by Systronics, Gujarat, India. Hardness tester (MHT-20) made by Campbell Electronics, Mumbai, India. Friability tester (FTA-20) Electrolab, Mumbai, India. Dissolution apparatus (DISSO-2000) made by Labindia, Mumbai, India. FTIR (Model no. 841) made by Perkin-Elmer, USA. DSC (DSC-50) Shimadzu, North America. Stability chamber made by Thermolab Scientific Equipments Pvt. Ltd., Mumbai, India.

Extraction of mucilage from *Aloe vera* leaves:

1 kg of fresh leaves were carved and mixed with 1 liter of water and centrifuged at 4000 rpm for 15 minutes. Distinct, mucilaginous solution was decanted. The obtained mucilage was washed with 250 ml of Ethanol, 250 ml of water and followed by 100 ml of Acetone. 725 g of mucilage was obtained by treating 1kg of leaves. (4)

Purification and drying of the *Aloe mucilage*

Purification is a crucial step during this work. The above obtained paste was mixed with trichloroacetic acid solution in 1:2 proportions. 1500 ml solution was reacted with 0.1N sodium hydroxide base adding slowly until precipitation was formed. To the above recovered 725 g of precipitate

100 ml of ethyl alcohol was added, followed by washing with 50 ml acetone and 50 ml diethyl ether. The obtained paste was dried by spreading on the open slabs. 700 g of powder was obtained by taking 725 g of above formed mucilage. From the above formed powder physical and chemical properties were studied and results are shown in **Table 1**.

Table 1: Physical and chemical characterization of *Aloe vera* mucilage dried powder

Property	<i>Aloe vera</i> powder
Appearance	Dark green powder
Solvability	When dissolved in water produces viscous solution
% yield (g /kg)	23 $\pm$ 2.173
Average particle size (μ m)	165.15 $\pm$ 10.265
% LOD	4.20 $\pm$ 2.573
Swelling ratio	45 $\pm$ 3.841
pH	6.5
Density of liquid (0.5% w/v)	0.997 $\pm$ 0.055
Microbial count (cfu/g)	Bacteria:6; Fungi: 3
Angle of repose	27.96 $\pm$ 1.684
Bulk density (g/cm ³)	0.604 $\pm$ 0.018
True density(g/cm ³)	0.706 $\pm$ 0.021
Carr's Index	14.447 $\pm$ 0.023
Hausner's ratio	0.855 $\pm$ 0.022

All values mentioned as mean $\pm$ S.D: No. of trials (n) = 3: S.D, Standard deviation

Compatibility studies

Differential Scanning Calorimeter (DSC)

This is done in order to study the melting points of the pure drug and pure polymers and also to study the changes that were produced when they are made in the form of a tablet. Heating rate of 10°C/min was maintained in nitrogen atmosphere by

taking a sample of 3 mg. The results are shown in Figures 1, 2. The DSC scan of eplerenone showed a short endothermic peak at 195.2 °C. The thermo gram with *Aloe vera* mucilage powder and povidone K30 showed endothermic peaks at 149 °C, 195.2 °C, 260 °C respectively.(5)

Figure 1: Differential Scanning Calorimetry of eplerenone pure drug

Figure 2: Differential Scanning Calorimetry of eplerenone with *Aloe vera* and povidone K30

Fourier Transform Infrared Spectroscopy

It can be used in order to study the compatibility of drug with polymers. In the present investigation by using FTIR individual spectrum of eplerenone and its

combinations with *Aloe* and Povidone K30 were studied. Spectrum results obtained are shown in Figures 3, 4, 5. All the characteristic peaks of eplerenone C=O-CH₃ stretching: 1272.43, -C=O Stretching: 1654.5, C=C Stretching: 1684.8, -OH

Stretching 3384.26 were found in the IR spectrums of eplerenone-polymers spectrum. This indicates the compatibility of eplerenone with the polymers used. It

shows that there were no chemical incompatibility between the drug and polymers used. (6)

Figure 3: Fourier Transform Infrared Spectrum of eplerenone pure drug

Figure 4: Fourier Transform Infrared spectrum of eplerenone with dried leaf mucilage of *Aloe vera*

Figure 5: Fourier Transform Infrared spectrum of eplerenone with povidone K30

Solubility analysis

In order to confirm the solubility of the drug it was made to dissolve in different solvents and it was found that eplerenone was soluble in dichloromethane, sparingly soluble in acetone and freely soluble in dilute NaOH and KOH solutions.

λ max of eplerenone

Eplerenone was found to be maximum at 245 nm and ratio of absorptivity was calculated which was less than 3%.

Estimation of eplerenone

50 mg of eplerenone was taken and mixed with 50 ml of 6.8 pH buffer, from the above solvent 1 ml was taken (1000 μ g/ml) and diluted to 10 ml in order to get 100 μ g/ml. Different dilutions were prepared ranging from 2.0 – 20.0 μ g/ml. The absorbance of the solutions was measured at 245 nm using UV-visible spectrophotometer. Standard curve was plotted by concentration versus absorbance and represented in Table 2. (7, 8)

Table 2: Standard curve data of eplerenone pure drug

Sl. No.	Conc (μ g/ml)	Absorbance
1	2	0.093 $\pm$ 0.001
2.	4	0.178 $\pm$ 0.001
3.	6	0.277 $\pm$ 0.012
4.	8	0.372 $\pm$ 0.021
5.	10	0.447 $\pm$ 0.035
6	12	0.544 $\pm$ 0.057
7	14	0.618 $\pm$ 0.039
8	16	0.711 $\pm$ 0.051
9	18	0.786 $\pm$ 0.016
10	20	0.870 $\pm$ 0.054

All values mentioned as mean $\pm$ S.D: Number of trials (n) = 3: S.D, standard deviation

Preparation of eplerenone matrix tablets using *Aloe*, Guar gum and povidone individually and in combination

Matrix tablets of eplerenone were prepared by using *Aloe* powder, guar gum and povidone K30. They were prepared by using different binder: tablet weight ratios viz. 1:20, 2:20, 3:20, 4:20 and 5:20. These agents were used as matrixing agents

along with other ingredients. The mentioned formulations were compressed by a direct compression technique using 8 mm flat faced punches. Dissolution studies were performed and formulations with *Aloe* and povidone showed better release. So, combination of *Aloe* and povidone were selected for further studies. The compositions of formulations are shown in Tables 3, 4. (9)

Table 3: Preparation of matrix tablets of eplerenone using three binders

Ingredients(mg)	Formulations				
	EPA1/ EPG1/ EPP1	EPA2/ EPG2/ EPP2	EPA3/ EPG3/ EPP3	EPA4/ EPG4/ EPP4	EPA5/ EPG5/ EPP5
Eplerenone	25	25	25	25	25
Binder*	10	20	30	40	50
Micro crystalline cellulose	162	152	142	132	122
Magnesium stearate	3	3	3	3	3
Total weight of tablet	200	200	200	200	200

* Binder means either *Aloe vera* dried mucilage powder (EPA), Guar gum (EPG) or Povidone K30 (EPP). EP represents Eplerenone.

Table 4: Preparation of matrix tablets of eplerenone using *Aloe vera* - povidone K30 combination

Ingredients (mg)	Formulation code				
	EPAP-1	EPAP-2	EPAP-3	EPAP-4	EPAP-5
Eplerenone	25	25	25	25	25
<i>Aloe vera</i> leaves dried mucilage powder	5	10	15	20	25
Povidone K-30	5	10	15	20	25
Micro crystalline cellulose	162	152	142	132	122
Magnesium stearate	3	3	3	3	3
Total weight of tablet	200	200	200	200	200

EPAP represents Eplerenone, aloe and Povidone K30.

Evaluation of matrix tablets:

The prepared tablets were studied for pre-compression and post-compression parameters. Pre-compression parameters results include Angle of Repose, Bulk

Density and Compressibility Index (Table 5). (10)

Table 5: Pre-Compression parameters for granules ready for compression

Name of Polymers	Angle of Repose	Bulk Density	Carr's Index	Hausner's Ratio
<i>Aloe vera</i> powder	27.96±1.684	0.704±0.040	14.12±2.876	1.165±0.039
Guar gum	38.72±1.115	0.750±0.023	16.88±5.935	1.179±0.040
Povidone K30	29.69±1.565	0.708±0.030	13.80±2.26	1.160±0.031
Blend ready for compression	26.36±0.369	0.718±0.614	15.2±0.691	1.369±0.264

Number of trials (n) = 5

Drug Release studies

In order to study the drug release, dissolution studies were performed by using USP dissolution apparatus II (paddle) with phosphate buffer pH 7.4 as the medium. The kinetic values produced from *in vitro* drug release profile of EPAP-1 – EPAP-5 are shown in Tables 6, 7. The

in vitro drug release kinetics of the formulations was depicted from the Figures 6, 7, 8. Linear regression graphs were plotted for EPAP 1- EPAP 5 and shown in Figures 9a, 9b, 9c and 9d. Since the formulation EPAP-5 was optimized it was compared with marketed tablets and shown in Figure 10.

Figure 6: Comparison of drug release among eplerenone matrix tablets prepared using *Aloe vera* (EPA1-EPA5)

Figure 7: Comparison of drug release among eplerenone matrix tablets prepared using Guar gum (EPG1-EPG5)

Figure 8: Comparison of drug release among eplerenone matrix tablets prepared using Povidone (EPP1-EPP5)

Figure 9 : Linear regression plots for the dissolution profile from EPAP-1-EPAP5 (a) Zero order plot (b) First order plot (c) Higuchi plot (d) Peppas's plot

Figure 10: Comparison of drug release profiles of the best among the optimized Eplerenone matrix tablets (EPAP-5) with marketed eplerenone tablet

Table 6: Kinetic values obtained from *In-Vitro* release profile of optimized eplerenone matrix tablets (EPAP)

Formulations	First order plot			Zero order plot		
	Slope (n)	K= -Slope x2.303	(r)	Slope (n)	K= -Slope	(r)
EPAP-1	-0.0007	0.001727	-0.97846	0.00355	0.003559	0.99039
EPAP-2	-0.0004	0.001128	-0.99684	0.00295	0.002955	0.99251
EPAP-3	-0.0015	0.003593	-0.97261	0.0099	0.009966	0.99661
EPAP-4	-0.0015	0.003524	-0.99259	0.00649	0.006498	0.98814
EPAP-5	-0.0017	0.004053	-0.98230	0.00670	0.006705	0.99525

Table 7: Additional kinetic values obtained from *In-Vitro* release profile of optimized eplerenone matrix tablets (EPAP)

Formulations	Higuchi's plot		Korsmeyer Peppas's plot	
	Slope (n)	(r)	Slope (n)	(r)
EPAP-1	1.72	0.971	0.162	0.930
EPAP-2	1.46	0.996	0.171	0.975
EPAP-3	3.10	0.985	0.287	0.947
EPAP-4	3.22	0.993	0.313	0.974
EPAP-5	3.30	0.993	0.304	0.968

Discussion

Matrix tablets of eplerenone, were prepared and these were found economical since a natural matrixing agent was used during the formulation. Different formulations were prepared using *Aloe vera*, guar gum and povidone. Optimized

formulation was selected based on the minimum drug release.

The endothermic peaks in DSC scan of eplerenone formulations with *Aloe vera* mucilage and povidone showed slight change in shifting towards the lower

temperature. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and polymers which lower the purity of each component in the mixture. The characteristic functional group peaks C-O-C, -CH, -C=C, C=O-CH₃, -OH, C=O of eplerenone in the FTIR spectra were not getting disturbed even after mixing with the polymers used indicating the suitability of the polymers used with eplerenone.

The matrix tablets that were formulated were studied for post compressional parameters and they were found within the range as per Pharmacopoeia specifications. Hardness and friability studies were performed on optimized formulation in order to study compactness and mechanical strength and they were within the acceptable range. Similarly from the uniformity content it was confirmed that the drug and polymer were mixed uniformly.

Matrix tablets of eplerenone prepared using combination of *Aloe vera* mucilage dried powder and povidone K-30 showed good swelling properties at first 2 hr and steady swelling in next 10 hr which indicates the uniformity of swelling of matrix tablets followed by drug release. From the drug release studies, it was clearly noticed that the increase in *Aloe vera* concentration decreases the drug release. Basing on the drug release kinetic studies it was found that the release was governed mainly due to diffusion and erosion mechanism as obtained from the values of regression coefficient (r) obtained from the graph. With regard to the optimized formulation EPAP-5 it was

found to be a zero order release pattern. Korsmeyer Peppas's plot indicates that almost all the formulations of eplerenone with *Aloe barbadensis* Miller leaf mucilage powder and povidone K30 matrix tablets followed Fickian release behavior.

The formulated matrix tablets of eplerenone using *Aloe* and povidone were studied for their derived properties, physical and chemical properties and *in-vitro* drug release studies. Almost all the formulations showed fairly acceptable values for all the parameters evaluated.

The formulation EPAP-5 matrix tablets were found to be suitable in order to provide 12 h drug release. The drug release was compared with the marketed tablets and found to be similar.

Conclusion

The main intention of this work is to check the suitability of *Aloe vera* as a matrixing agent which can retard the drug release for prolonged period of time. The drug release was found to be decreased by increasing the concentration of *Aloe*. *Aloe vera* alone was tried during the formulation but when it was combined with Povidone K-30 it made a great change in the drug release pattern and also produced prolonged action. Hence not only eplerenone matrix tablets can be made with *Aloe vera* but also other drugs could be made into matrix tablets.

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