Original Article

"In Vitro Evaluation Of Eplerenone Controlled Release Tablets"

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INTRODUCTION

Controlled release oral drug delivery systems have been an integral part of pharmaceutical technology for several decades. Within the pharmaceutical industry delivery systems and formulations have been developed which can provide a wide variety of drug release profiles, including systems designed for immediate, continuous, pulsatile and delayed administration. In recent years, much of the focus in oral controlled-release technology has been directed towards site-specific delivery in the GI tract, chronobiology as related to oral delivery systems and the development of technology to control the release and delivery of non-traditional drug candidates, i.e. peptides and proteins. Included in these various technologies are osmotically controlled devices, matrix tablets, hydrogels, polymeric systems, multi particulates and erosion systems regulated by geometric design. In spite of the availability of numerous technologies to achieve up to 24 h controlled drug release, relatively few products that are efficacious for once-a-day dosing have reached the market. One of the problems associated with these products is poor colonic drug absorption that limits the once daily efficacy of dosage forms.

METHODOLOGY:

EVALUATION OF MATRIX TABLETS:

Pre-Compression Parameters:

1.Angle of Repose:

Table 6.7: Angle of repose of polymers

Parameter	Trial	*Aloe barbadensis miller* leaves mucilage	Gaur gum	Povidone
Angle Of repose (⌟⌞)	1	29.45	39.55	30.59
	2	28.20	38.25	27.55
	3	25.26	38.05	29.85
	4	27.62	37.54	31.58
	5	29.25	40.21	28.79
Mean		**27.96±1.684**	**38.72±1.115**	**29.69±1.565**

Number of trials (n) = 5

2. Loose Bulk Density (LBD):

Table 6.8: Loose Bulk density of polymers

Parameter	Trial	*Aloe barbadensismiller* leaves mucilage	Gaur gum	Povidone
	1	0.62	0.63	0.58
	2	0.58	0.65	0.60
	3	0.59	0.61	0.62
	4	0.62	0.65	0.59
	5	0.61	0.64	0.66
Mean		**0.604±0.018**	**0.636±0.018**	**0.61±0.032**

Number of trials (n) = 5

3.Tapped Bulk density (TBD):

Table 6.9: Tapped Bulk density of polymers

Parameter	Trial	*Aloe barbadensismiller* leaves mucilage powder	Gaur gum powder	PovidonePowder
	1	0.75	0.73	0.69
	2	0.64	0.79	0.72
	3	0.70	0.75	0.71
	4	0.72	0.74	0.67
	5	0.71	0.74	0.75
Mean		**0.704±0.040**	**0.750±0.023**	**0.708±0.030**

Number of trials (n) = 5

4. Carr's Index:

Table 6.10: Carr's Index of polymers

Parameter	Trial	*Aloe barbadensis miller* leavesmucilage	Gaur gum	Povidone
	1	17.3	13.6	15.9
	2	09.6	26.5	16.6
	3	15.7	18.7	12.6
	4	13.9	12.1	11.9
	5	14.1	13.5	12.0
Mean		**14.12±2.876**	**16.88±5.935**	**13.80±2.26**

Number of trials (n) = 5

5. Hausner Ratio:

Table 6.11: Hausner Ratio of polymers

Parameter	Trial	*Aloe barbadensismiller* leaves mucilage powder	Gaur gumpowder	Povidonepowder
	1	1.209	1.159	1.189
	2	1.103	1.215	1.200
	3	1.186	1.229	1.145
	4	1.161	1.138	1.131
	5	1.164	1.156	1.136
Mean		**1.165±0.039**	**1.179±0.040**	**1.160±0.031**

Number of trials (n) = 5

Post-Compression Parameters:

1. General Appearance of Tablets:

The formulated tablets were circular shape and white to yellowish brown colour for all the formulations. There were little or no manufacturing defects in the tablets. Surface was elegant, smooth and uniform.

2.Thickness and diameter:

Table 6.12: Mean thickness of Eplerenone matrix tablets

Parameter	Formulation	EPA Matrixtablets	EPG matrixtablets	EPP matrixtablets	EPAP matrixtablets
	1	3.52±0.068	3.49±0.368	3.65±0.254	3.64±0.157
	2	3.71±0.125	3.55±0.124	3.68±0.124	3.51±0.125
	3	3.65±0.214	3.62±0.231	3.84±0.235	3.62±0.154
	4	3.55±0.089	3.33±0.014	3.65±0.168	3.65±0.212
	5	3.57±0.078	3.39±0.235	3.51±0.114	3.55±0.245

All values mentioned as mean ± S.D; Number of trials (n) = 3

3.Uniformity of Weight Test:

Table 6.13: Mean Weights of Eplerenone matrix tablets.

Parameter	Formulation	EPA Matrix tablets	EPG matrix tablets	EPP matrix tablets	EPAP Matrix Tablets
Weightof the (mg tablet)	1	201.25±05.8	202.31±17.5	199.56±06.4	200.50±5.6
	2	199.34±06.1	200.10±04.5	199.65±05.8	200.65±5.2
	3	198.56±02.4	200.45±08.5	198.25±06.5	198.96±6.4
	4	198.98±07.4	199.80±06.4	201.32±03.6	199.70±4.4
	5	199.35±06.6	199.65±09.6	202.01±05.2	199.85±5.6

5. Friability Test:

Table 6.14: Mean Friability of Eplerenone matrix tablets.

Parameter	Formulation	EPA Matrix tablets	EPG matrix tablets	EPP matrix tablets	EPAP matrix tablets
	1	0.230±0.03	0.350±0.25	0.350±0.04	0.590±0.09
	2	0.560±0.05	0.850±0.06	0.680±0.05	0.640±0.08
	3	0.550±0.05	0.470±0.09	0.480±0.02	0.680±0.01
	4	0.680±0.03	0.540±0.01	0.660±0.07	0.810±0.09
	5	0.690±0.02	0.210±0.03	0.380±0.04	0.490±0.03

All values mentioned as mean ± S.D; Number of trials (n) = 3

8. *In vitro* Drug Release Studies from Matrix tablets

The *in-vitro* dissolution was studied in phosphate buffer pH 7.4. The *in-vitro* dissolution studies were carried out in triplicate and the results shown in the tables were mean of replicate values. *In-vitro* release data obtained for matrix tablets were tabulated. The results of *in-vitro* dissolution

studies obtained in these formulations were plotted in five models of data treatments as follows. Cumulative percentage of drug released Vs. Time.Log cumulative % of drug retained Vs. Time. Cumulative % of drug released Vs. Square root of time (Higuchi's plot). Log cumulative percentage of drug released Vs. Log time(Korsmeyer Peppa‘s plot) (% Drug Retained) $^{1/3}$ Vs. Time (Hixson Crowell‘s plot). The plot of cumulative percentage of drug released as a function of time for different Eplerenone matrix tablets (Zero order release). Cumulative percentage drug released has been found 99.2, 98.9, 99.85, 99.1 and 88.64 for the matrix tablets EPAP-1, EPAP-2, EPAP-3, EPAP-4 and EPAP-5 respectively at the end of 12 h. *In-vitro* dissolution studies clearly showed that the Eplerenone containing *Aloe barbadensis miller* leaves mucilage showed good controlled release patterns as compared to Guar gum and Povidone. Attempts were made to fit the data to study order of release. A first order release would be predicted by equation given below

Log W = log WO – Kt/ 2.303Where,

W = Amount of drug remained in matrix.Wo = Initial amount of drug in matrix.

K = First order rate constant.T= Time.

Similarly, zero order release would be predicted by equation given below

dCs/dt = Ko

Where, CS = Concentration of the drug present in the matrix. KO = Proportionality factor i.e. reaction rate constant.T = Time

Since Cs is a constant, x - the amount of drug released can be described as in

equation:

dx/dt=k Integration of equation yields

X = kt + t constant

If the plot of log cumulative percentage remaining v/s time yields a straight line, the release follows first order kinetics. Similarly, the plot of cumulative percentage released v/s time, if yields a straight line, the release follows zero order kinetics.

the plot of log cumulative % drug retained vs. time (First Order) for different formulation of EPAP matrix tablets. Since these plots did not yield a straight line, the data was subjected to linear regression analysis (r), the results of which were shown intable. 4.46. The 'r' values obtained for first order kinetics were found to be - 0.97846, -0.99684, -0.97261, -0.99259 and 0.9823 for formulations GPAP-1 to GPAP-5 respectively. And those for zero order kinetics 0.99039, 0.992511, 0.99661, 0.988149 and -0.995252 for formulations EPAP-1 to EPAP-5 respectively. Since greater degree of association best fitted with zero order kinetic models. It can be concluded that, all the matrix tablets followed zero order kinetics as the release pattern of the drug. The rate constant of first order release was calculated from the slope value bymultiplying with 2.303. The rate constant for zero order plots can be obtained by using equation KO = -slope The data when treated according to Higuchi's diffusion equation (Q=Kt indicated that the formulations released the drug by diffusion. Higuchi's plot and regression values given were 0.971738, 0.996448, 0.98504, 0.993489 and 0.993936 for EPAP-1 to EPAP-5 respectively

Further to know the release pattern of Eplerenone from matrix tablets, the results were analyzed according to Korsmeyer

Peppa‘s exponential

$q = Kt^n$

Where, q is fraction of drug released up to time (t), k denotes a constant, 'n' is thereleased exponent indicative of the mechanism of release.

The slope 'n' was computed to know whether the release was

Fickian or non-Fickian. For non-Fickian release (_n' values=0.5to 1.0), while for Fickian diffusion (_n' value= 0.5).
The slope values for Eplerenone matrix tablets were tabulated. The values were 0.162456, 0.171559, 0.287578, 0.313169 and 0.304558 for formulation EPAP-1 to
EPAP-5. The values of 'n' were less than 0.5 for all the formulations. So, all formulations follow the Fickian release.

The *in-vitro* release data was further plotted as $(1\text{-}mt/m)^{1/3}$ v/s

Time proposed by Hixson Crowell's to verify whether the drug release is by erosion mechanism and it can be represented as

$$\sqrt[3]{1 - mt/m} = Kt$$

Where mt = Drug release at time t
m = Drug originally present in the tablet

The regression coefficient values of the plots for different matrix tablets. The 'r' values were found to be -0.98355, -0.99574, -0.98517, -0.99441 and -0.99214 for formulations EPAP-1 to EPAP-5 respectively. The above observations showed that the drug release from different matrix tablets fitted well to the *erosion mechanism*. The slope of line indicated that the rate of disappearance of the tablets by erosion. The slope was calculated and it was found to be -0.00043, -0.0003, -0.00084, -0.00083 and -0.00092 formatrix tablets EPAP-1 to EPAP-5 respectively.

Table 6.15: *In-Vitro* Dissolution Profile of optimized Eplerenone matrix tablets (EPAP-1)

Time (h) T	*ROOT T*	*LOGT*	Cum. Drug Released (mg)	Cum. % Drug Released	Log Cum. % Drug Released	Cum. % Drug Remained	Log Cum. % Drug Remained	(% Drug Retained)$^{1/3}$
0	0	0	0	0	0	100	2	4.64159
1	1.000	0.000	4.51±0.14	45.08046	1.653988	54.91954	1.739727	3.80109
2	1.414	0.301	4.97±0.15	49.66921	1.696087	50.33081	1.701834	3.69232
4	2.000	0.602	5.19±0.16	51.88552	1.715046	48.11448	1.682276	3.63713
6	2.450	0.778	5.58±0.19	55.84322	1.746971	44.15678	1.644997	3.53454
8	2.830	0.903	5.93±0.25	59.37563	1.773608	40.62437	1.608787	3.43765
10	3.160	1.000	6.41±0.29	64.08736	1.806772	35.91264	1.555247	3.29920
12	3.460	1.079	7.08±0.23	70.79448	1.849999	29.20552	1.465465	3.07955

Table 6.16: *In-Vitro* Dissolution Profile of optimized Eplerenone matrix tablets (EPAP-2)

Time (h) T	*ROOT T*	*LOGT*	Cum. Drug Released (mg)	Cum. % Drug Released	Log Cum. % Drug Released	Cum. % Drug Remained	Log Cum. % Drug Remained	(% Drug Retained)$^{1/3}$
0	0	0	0	0	0	100	2	4.64159
1	1.000	0.000	3.68±0.12	36.8046	1.565902	63.1954	1.800685	3.98317
2	1.414	0.301	4.10±0.53	41.08069	1.613638	58.91931	1.770258	3.89122
4	2.000	0.602	4.41±0.16	44.13149	1.644749	55.86851	1.747167	3.82286
6	2.450	0.778	4.77±0.15	47.66851	1.678232	52.33149	1.718763	3.74042
8	2.830	0.903	5.15±0.72	51.46644	1.711524	48.53356	1.686042	3.64765
10	3.160	1.000	5.44±0.12	54.37816	1.735425	45.62184	1.659173	3.57320
12	3.460	1.079	5.71±0.27	57.08414	1.756515	42.91586	1.632618	3.50111

Table 6.17: *In-Vitro* Dissolution Profile of optimized Eplerenone matrix tablets (EPAP-3)

Time(h) T	*ROOT T*	*LOGT*	Cum. Drug Released (mg)	Cum. % Drug Released	Log Cum. % Drug Released	Cum. % Drug Remained	Log Cum. % Drug Remained	(% Drug Retained)$^{1/3}$
0	0	0	0	0	0	100	2	4.64159
1	1.000	0.000	3.96±0.15	39.56322	1.597292	60.43678	1.781301	3.92434
2	1.414	0.301	4.51±0.22	45.13126	1.654477	54.86874	1.739325	3.79992
4	2.000	0.602	5.20±0.25	52.0154	1.716132	47.98461	1.681102	3.63385
6	2.450	0.778	5.86±0.96	58.61908	1.768039	41.38092	1.6168	3.45886
8	2.830	0.903	6.80±0.28	68.0423	1.832779	31.95775	1.504576	3.17340
10	3.160	1.000	7.24±0.28	72.38161	1.859628	27.61839	1.441198	3.02273
12	3.460	1.079	8.35±0.88	83.53931	1.921891	16.46069	1.216448	2.54379

Table 6.18: *In-Vitro* Dissolution Profile of optimized Eplerenone matrix tablets (EPAP-4)

Time (h) T	*ROOT T*	*LOGT*	Cum. Drug Released (mg)	Cum. % Drug Released	Log Cum. % Drug Released	Cum. % Drug Remained	Log Cum. % Drug Remained	(% Drug Retained)$^{1/3}$
0	0	0	0	0	0	100	2	4.64159
1	1.000	0.000	3.62±0.95	36.22989	1.559067	63.77011	1.804617	3.99520
2	1.414	0.301	4.66±0.85	46.59218	1.668313	53.40782	1.727605	3.76589
4	2.000	0.602	5.26±0.25	52.57172	1.720752	47.42828	1.676037	3.61975
6	2.450	0.778	5.99±0.28	59.8708	1.777215	40.12922	1.60346	3.42363
8	2.830	0.903	7.07±0.34	70.68598	1.849333	29.31402	1.467075	3.09867
10	3.160	1.000	7.42±0.31	74.24713	1.87068	25.75287	1.410826	2.95308
12	3.460	1.079	8.13±0.27	81.28529	1.910012	18.71471	1.272183	2.65498

Table 6.19: *In-Vitro* Dissolution Profile of optimized Eplerenone matrix tablets (EPAP-5)

Time (h) T	*ROOT T*	*LOGT*	Cum. Drug Released (mg)	Cum. % Drug Released	Log Cum. % Drug Released	Cum. % Drug Remained	*Log Cum. % Drug Remained*	(% Drug Retained)$^{1/3}$
0	0	0	0	0	0	100	2	4.6
1	1.000	0.000	3.87±0.12	38.75862	1.588368	61.24138	1.787045	3.94168
2	1.414	0.301	4.73±0.19	47.30713	1.674927	52.69287	1.721752	3.74901
4	2.000	0.602	5.56±0.25	55.59241	1.745016	44.40759	1.647457	3.54101
6	2.450	0.778	6.25±0.28	62.46161	1.795613	37.53839	1.574476	3.34831
8	2.830	0.903	6.92±0.31	69.16414	1.839881	30.83586	1.489056	3.13582
10	3.160	1.000	7.75±0.31	77.53678	1.889508	22.46322	1.351472	2.82156
12	3.460	1.079	8.56±0.41	85.64161	1.932685	14.35839	1.157106	2.43053

Table 6.20: Kinetic Values Obtained from *In-Vitro* Release Profile of optimized Eplerenone Matrix Tablets (EPAP)

Formulations	First Order Plot			Zero Order Plot		
	Slope (n)	First Order Rate ConstantK= -Slope x 2.303	Regression Co-efficient (r)	Slope (n)	Zero Order Rate ConstantKo=-Slope	Regression Co-efficient (r)
EPAP-1	-0.00075	0.001727	-0.97846	0.003559	0.003559	0.99039
EPAP-2	-0.00049	0.001128	-0.99684	0.002955	0.002955	0.992511
EPAP-3	-0.00156	0.003593	-0.97261	0.009966	0.009966	0.996610
EPAP-4	-0.00153	0.003524	-0.99259	0.006498	0.006498	0.988149
EPAP-5	-0.00176	0.004053	-0.98230	0.006705	0.006705	0.995252

Table 6.21: Kinetic Values Obtained from *In-Vitro* Release Profile of optimized Eplerenone Matrix Tablets (EPAP)

FORMULATION	**Higuchi's**		**Korsmeyer Peppa's**		**Hixson-Crowell's**	
	Slope (n)	**Regression Co-efficient (r)**	**Slope (n)**	**Regression Co-efficient (r)**	**Slope (n)**	**Regression Co-efficient (r)**
EPAP-1	1.725046	0.971738	0.162456	0.93021	-0.00043	-0.98355
EPAP-2	1.465816	0.996448	0.171559	0.975678	-0.00030	-0.99574
EPAP-3	3.103433	0.98504	0.287578	0.947932	-0.00084	-0.98517
EPAP-4	3.227632	0.993489	0.313169	0.974429	-0.00083	-0.99441
EPAP-5	3.308515	0.993936	0.304558	0.968565	-0.00092	-0.99214

Fig 6.10: Zero order plots of Eplerenone -*Aloe barbadensis miller* leaf mucilage matrix tablets (EPA1-EPA5)

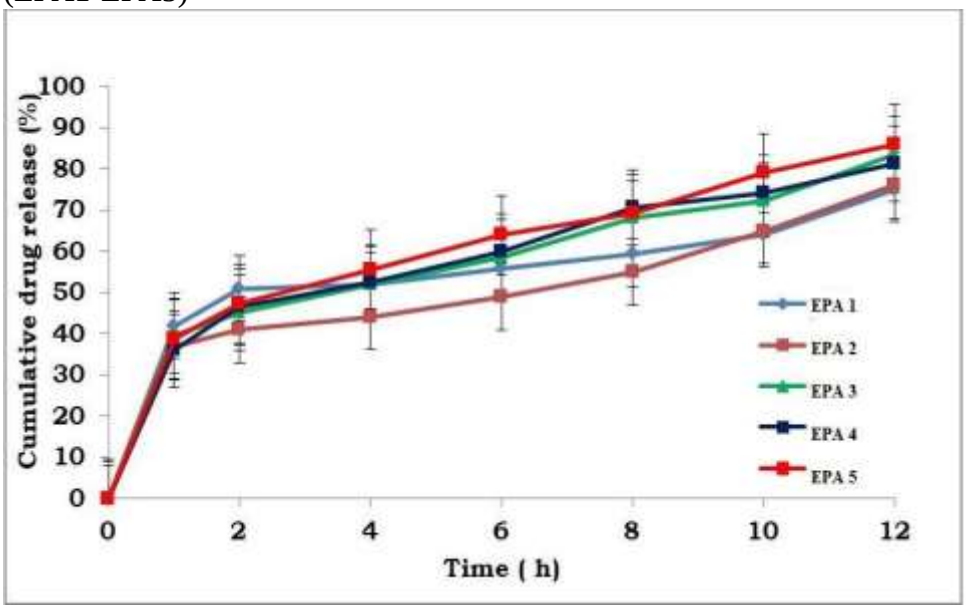


Fig 6.11: Zero order plots of Eplerenone -Guar gum matrix tablets (EPG1-EPG5)

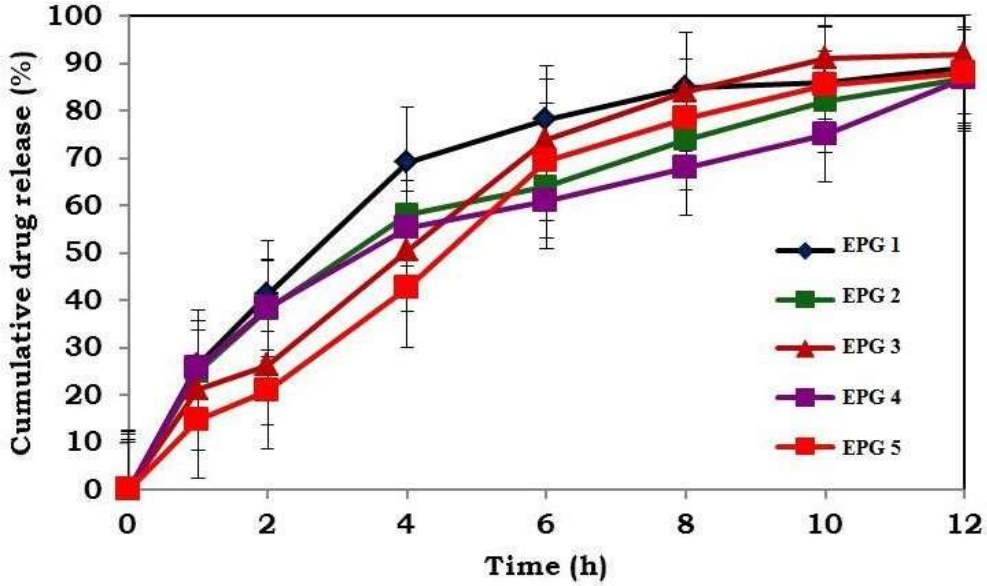


Fig 6.12: Zero order plots of Eplerenone -Povidone matrix tablets (EPP1-EPP5)

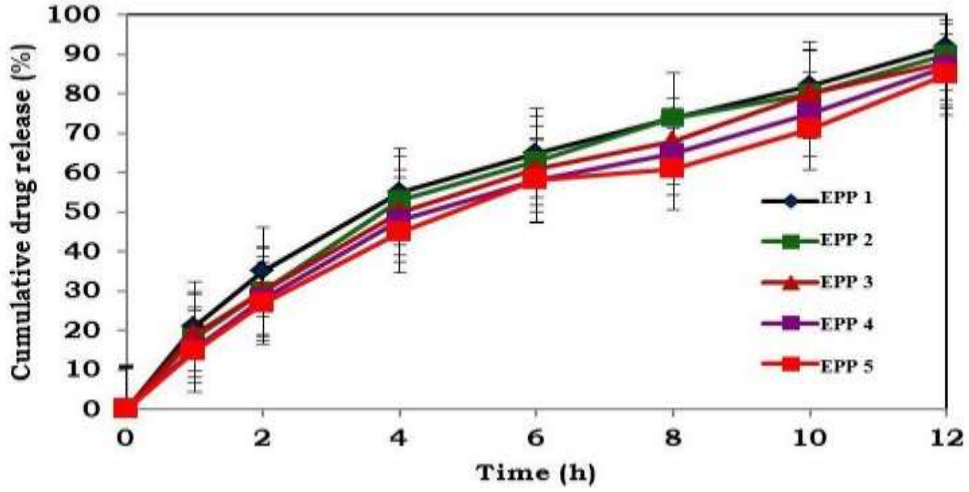


Fig 6.13: Zero order plots of optimized Eplerenone *Aloe barbadensis miller* and Povidone matrix tablets

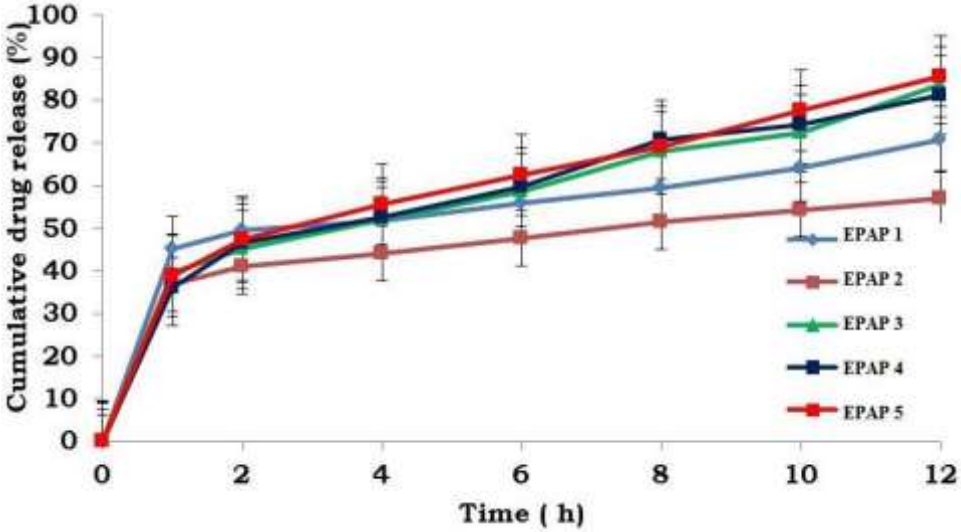


Fig 6.14: First order plots of optimized Eplerenone -*Aloe barbadensis miller* mucilage andPovidone matrix tablets

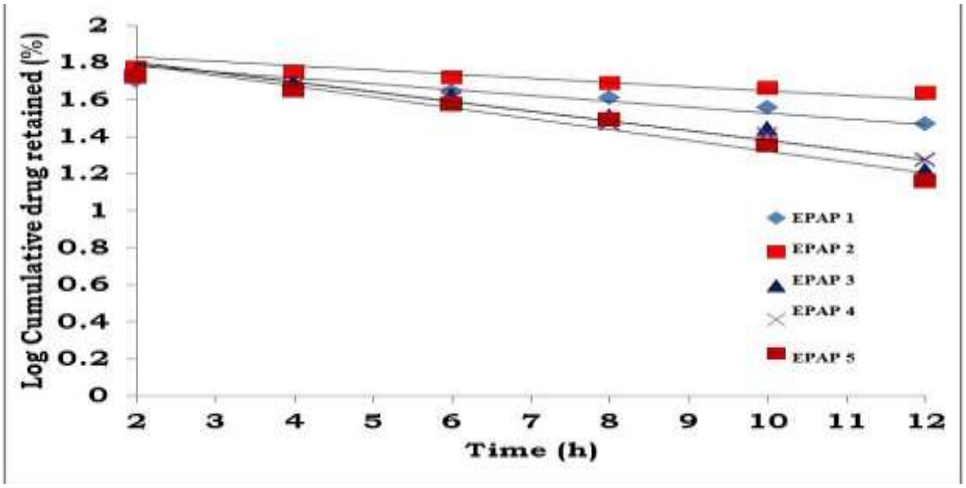


Fig 6.15: Higuchi's Plots of optimized Eplerenone *Aloe barbadensismiller* mucilage and Povidone matrix tablets

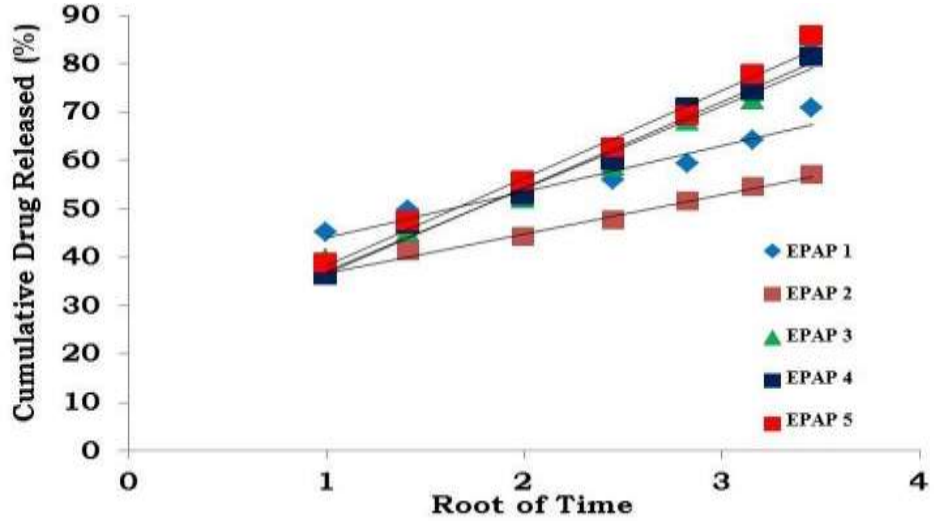


Fig 6.16: Korsmeyer Peppa's Plots of optimized Eplerenone - *Aloe barbadensis miller* mucilage and Povidone matrix tablets

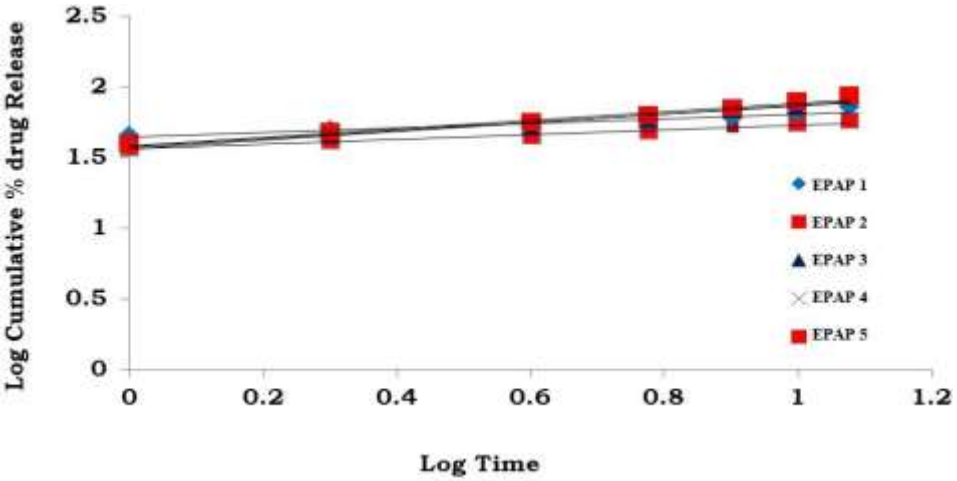
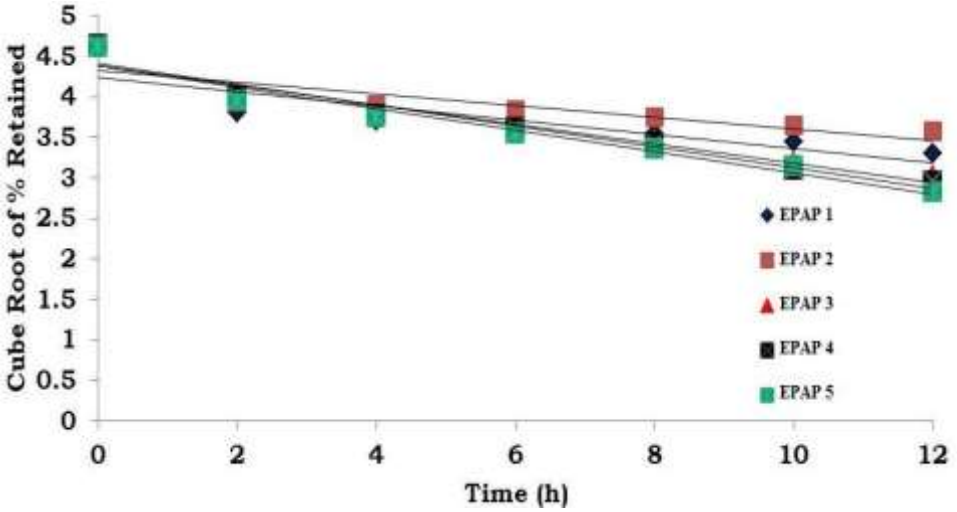
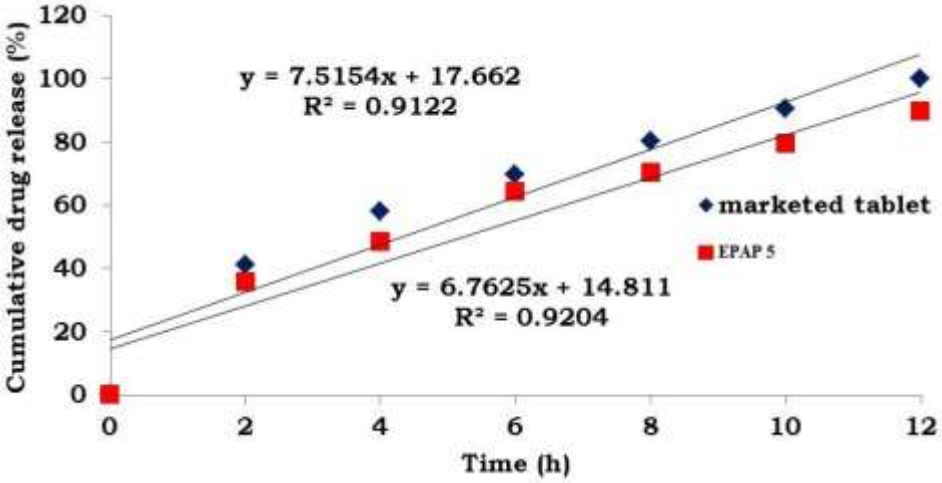


Fig 6.17: Hixson Crowell's Plots of optimized Eplerenone - *Aloe barbadensis miller* mucilage and Povidone matrix tablets



9. Comparison of *In vitro* release profile of selected formulation with marketed formulation

Fig 6.18: Plot of cumulative % drug released vs. time for profiles of the best among the optimized Eplerenone matrix tablets (EPAP-5) with marketed Eplerenone tablet.



Summary of Matrix Tablets

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drugdelivery systems.

AN Eplerenone, have been chosen as a model drug in the formulation of matrix tablets drug delivery systems for the present work.

The formulated matrix tablets are economical to alter beneficially theproperties of the existing drugs than developing new drug entities.

For the above formulations, *Aloe barbadensis miller*, Guar Gum,Povidone were blended in varying proportions of Eplerenone.

UV spectrums of pure Eplerenone and in formulations showed λ max at 245 nm, indicates that there was no negative interaction of Eplerenone with the excipientsused.

The endothermic peaks in DSC scan of Eplerenone formulations with *Aloe barbadensis miller* leaves mucilage, *Ficus carica* and *Ficus glomerata* fruit mucilagesand 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 of Eplerenone in the FTIR spectrums were not getting disturbed even after mixing with the polymersused indicates the suitability of the polymers used with Eplerenone.

Matrix technique is gaining an importance in current days as a simplest technique for a controlled release of drugs. If a drug has right mix of physical chemistry and pharmacology, matrix tablets have a wide range of advantages. Many researches are aimed to discover an economical and effective polymer to release drug by this system. After preparation of matrix tablets, physicochemical studies, in vitro release studies, in vivo release studies, human studies and stability studies were performed. But all the prepared andevaluated matrix tablets must receive approval from FDA before sale.

The aim of this study was to explore the feasibility of matrix tablets of Eplerenone.

A satisfactory attempt was made to develop matrix tablets by using economical, easilyavailable and

natural polymer *Aloe barbadensis miller* leaves mucilage.
From the reproducible results obtained from the executed experiments it can beconcluded that:
Biocompatible and natural polymers like *Aloe barbadensis miller* leaf mucilage can be used to formulate matrix tablets of Eplerenone
The release of Eplerenone from the formulations is retarded as the proportions of *Aloe barbadensis miller* leaves mucilage increased
In vitro drug release studies showed a steady release of Eplerenone from the formulated matrix tablets.
Formulations EPAP-5 E showed a better controlled release
The formulation EPAP-5 matrix tablets showed a kinetic release profile similar to the theoretical controlled release Profile of the drug and could be regarded as the optimumformulation.

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