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Formulation and *In-Vitro* Evaluation of Eplerenone Fast Disintegrating Tablets by Solid Dispersion technique

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ABSTRACT

Eplerenone, a BCS class II drug with low bioavailability and $t_{1/2}$ of 3-6 hrs is primarily used to treat Congestive Heart Failure (CHF) and hypertension. So, to develop the biological performance of Eplerenone, solid dispersion along with oral disintegrates was prepared by employing HP β-Cyclodextrin and β-Cyclodextrin. Eplerenone solid dispersions were repared with various carriers in varying ratios of carrier and drug respectively (0.5:1, 1:1 and 1.5:1). Results of prepared Eplerenone solid dispersions through solvent evaporation technique were demonstrated which comprise melti g point determination, solubility, entrapment efficiency, drug content uniformness and *in-vitro* breakup studies. Characterization of solid state was done by FT-IR. From comparison of all the formulation characteristics, formulation (F3) containing Eplerenone + Hp β-cyclodextrin (1:1.5) showed better results y solvent evaporation technique. As maximum drug was released from F3 at the end of 60 min, this formulation was decided as the best. From the optimized formulation, Fast dissolving tablets were formulated employing various disintegrates in varying concentrations. The pre and post compression parameters were calculated and the results were pecified. All the results were within the acceptable range. An *in-vitro* drug discharge study of the formulated drug was done victimisation pH 6.8 buffers. F6 formulation containing crospovidone (13.5mg) exhibited 97.36 % drug release within 20mins. The optimized formulation follows zero-order release kinetics.

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INTRODUCTION

The novel technology going from fast-disintegrating formulations known as fast dissolve, speedy dissolve, fast melt and active disintegrating tablets. Solid Dispersion has been proved with as platform technology the formulation of ailling soluble drugs [1]. Specifically, Solid Dispersion technology out of date applicable to well up formulations having a high drug using a high tendency to form into crystals. Eplerenone is primarily used to treat Congestive Heart Failure (CHF) and hypertension can be treated from BCS class II medicine like Eplerenone. It has low absolute bioavailability. To enhance the biological performance of Eplerenone solid disper-

sion with fast dissolving tablet was formulated by using β-Cyclodextrin, HP β-Cyclodextrin. Optimization of the best formulation used to be done at the origin of medicine release time [2].

MATERIALS & METHODS

Eplerenone became purchased free of charge sample from B.M.R. Chemicals, Hyderabad, India; HP β-Cyclodextrin & β-Cyclodextrin, was once purchased from S.D. Fine Chemicals, Anantapur, India, Crosspovidone, Sodium starch glycolate (SSG), microcrystalline cellulose, Magnesium stearate used to be a present sample of Bliss chemicals & pharmaceuticals India Ltd., Mumbai, India. Methanol was purchased from LOBA chemicals, Kadapa, India and other ingredients victimised in with Analytical grade.

Methodology

Compatibility studies

Sample concentration in KBr must be within the limits of 0.2% to 1%. The thickness of the pellet is much greater than a liquid film, so sample with low concentration is required [3]. Too high concentration generally leads to difficulties in obtaining clear pellets.

Preparation of solid dispersions of Eplerenone

In solvent evaporation technique, the drug and carriers were mixed in drug and HP β-Cyclodextrin, β-Cyclodextrin 1:0.5, 1:1 and1:1.5 ratios in methanol. Spectacular Solvent becomes taken away via evaporation under remittent pressure [4]. Them was pulverised and passed through sieve # 60. And now the obtained product was collected.

Evaluation of Solid Dispersions

Drug Content

A quantity, which was equivalent to 25 milligram of drug used to be weighed accurately and so transmitted to 100 ml volumetrical flask. The quantity need on top of things using pH 6.8 buffer and agitated for 10min to make sure complete potency of your drug [5]. The absorbance was measured at 255 nm for Eplerenone in UV-Visible spectrophotometer.

Entrapment efficacy

The prepared Eplerenone solid dispersion dissolved in distilled water was kept in centrifuge for 40min at a speed of at 10^{o}C [6].

Spectacular absorbance of the respective sample given up palmy UV Visible spectrophotometer at λ_{max} of 255 nm.

$$Entrapment \quad Efficiency = \frac{The\ total\ amount\ of\ drug - Free\ drug}{The\ total\ amount\ of\ drug} \times 100$$

The absorbance of the current solution used to be measured at 255 nm.

In vitro dissolution study

Dissolution test used to be done using Paddle method it involveing pH 6.8 polisher serve dissolution medium and that used to be services at temperature of 37$\pm$1^{o}C. At regular intervals of time, 5ml of sample were drawn from the apparatus which was then filtered [7]. Later replacement with 5ml of fresh dissolution medium was done.

Kinetics of Drug Discharge

The suppressant mechanism for Eplerenone solid dispersions decided using Zero-order and first-order [8].

Zero-order: Q=Ko t

First-order: Log Q= Log Qo-K1 t/2.303.

Formulation of Eplerenone Tablets

Equivalent weight of Eplerenone was added with suitable excipients and the tablets were formulated using direct compression technique. Each ingredient was passed through (#40 mesh) sieves individually (Table 1). The drug and Micro crystalline Cellulose were gradually blended by addition of small quantity of each at a time to come and blend it to procure a consistent mixture and this used to be kept aside [9].

Pre-compression Parameters

Preparation of Mixed Blend of Drug & Excipients

The powdered blend was analyzed for flow properties as follows.

Angle of repose: θ = $\tan^{-1}$ (h/r)

Bulk density = Weight of powder/ Bulk volume

Tapped density = Weight of powder/ Tapped volume

Carr's Index (I) = (Tapped Density - Bulk Density)/ (Tapped Density) x100

Hausner's ratio = Tapped density/ Bulk density

Valuation of Tablets

Weighting variation test

The assessment was performed to make sure. First, the total volume going from twenty tablets from every formulation decided and was determined and finally average turned into calculated [10].

Drug content uniformity

At Random, 20 tablets have been grassed, reweighed & made within powder. Similar to 25 mg used to be weighed exactly and subsequent molten in 100ml of 0.1N HCl and so solution turned into agitated carefully [11].

Table 1: Formulation of Eplerenone Tablets

Ingredients	F1	F2	F3	F4	F5	F6
Eplerenone (weight equivalent to 25 mg)	35	35	35	35	35	35
Crospovidone	4.5	9	13.5	-	-	-
SSG	-	-	-	4.5	9	13.5
MCC	104.5	100	95.5	104.5	100	95.5
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total	150	150	150	150	150	150

Tablet hardness

The pressure was gradually increased for breaking the tablet [11]. All the values were expressed in terms of Mean and SD. The acquired hardness was stated in terms of kg/sq.cm. Hardness Limits: 4-6kg/sq.cm.

Tablet friability

Friability test was performed to predict the tablet ability to endure any abrasions in packaging, handling & in transport. Roche friabilator, a commonly used instrument was routine watch over friability of the tablets. 20 tablets have been reweighed from each and every batch and situated in friabilator and set to rotate at an rpm of 25 for 4 min [12]. All the tablets were de-dusted and weighed again. The percentage of friability was calculated using the formula.

Friability=

$$\frac{weight\ of\ tablet\ before\ test - weight\ of\ tablet\ after\ test}{weight\ of\ tablet\ before\ test} \times 100$$

Thickness and Diameter

5 tablets were taken and their thickness was measured with the help of Vernier calipers [13].

Dissolution studies

It was carried out by employing Paddle type Apparatus at 50rpm. The 900 ml of pH 6.8 buffer served as dissolution medium was serviced at 37±0.5°C [13]. An equivalent quantity of fresh dissolution medium was replaced without delay subsequent to withdrawal of test sample.

In-Vitro Disintegration study

For testing disintegration time of tablets, 1 tablet was kept in each tube and basket rack was positioned in a 1 lit beaker filled with pH6.8 buffer solution at 37°C±1°C so that spectracular tablet remains 25mm underneath the surface of the liquid. Tablet disintegration time was noted [14].

Release kinetics

The Fast Disintegrating Eplerenone tablets drug release data were analyzed mathematically according to the following models [15]. Zero-order- Q=Ko t; First-order- Log Q= Log Qo-K1 t/2.303.

RESULTS AND DISCUSSION

Compatibility study

From drug excipient compatibility trend analysis, we referred to absence of interactions in between pure drug and excipients as shown in Figures 1 and 2.

Drug Content

Drug content of the formulated solid dispersions was turned out to be within the limits of 62.2-93.75% respectively (Table 2).

Entrapment efficacy

The entrapment efficacy of formulated solid dispersions was turned out to be within the range of 69.14-82.63% respectively (Table 2).

In-Vitro dissolution studies

The Eplerenone solid dispersions with HP β Cyclodextrin in various ratios were observed which shows at the end of 60mins (Table 3) the formulation F1 releases 80.63, formulation F2 releases 83.96, F3 releases 96.42, formulation F4 releases 72.42, Formulation F5 releases76.56, and formulation F6 releases 83.45%.

In-vitro drug release kinetics studies for best formulation F3

On comparing release kinetics analysis of best formulation, i.e. F3 with zero-order & first order, we could confirm that F3 stick to first-order release kinetics studies with R^2 value 0.915 whereas zero-order release kinetics studies with R^2 value 0.750. Hence, R^2 values prove that F3 follows first-order release kinetics.

Evaluation of Epleronone Fast disintegrating Tablets

The angle of repose, bulk density, Tapped density, Carr's index and Hausner's ratio further revealed that the blends have good flow nature (Table 4).

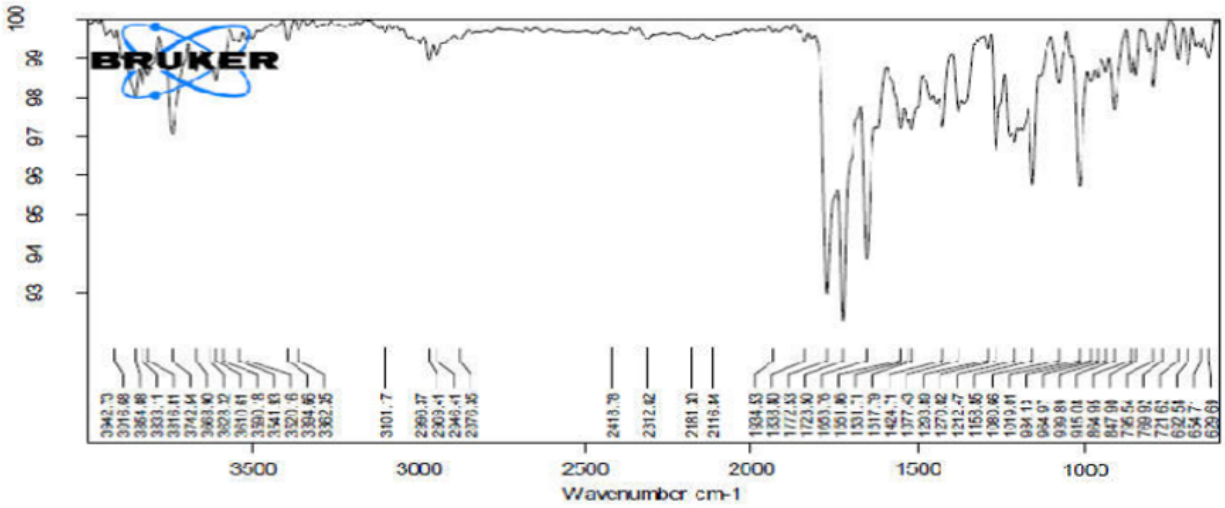

Figure 1: IR spectrum of Eplerenone

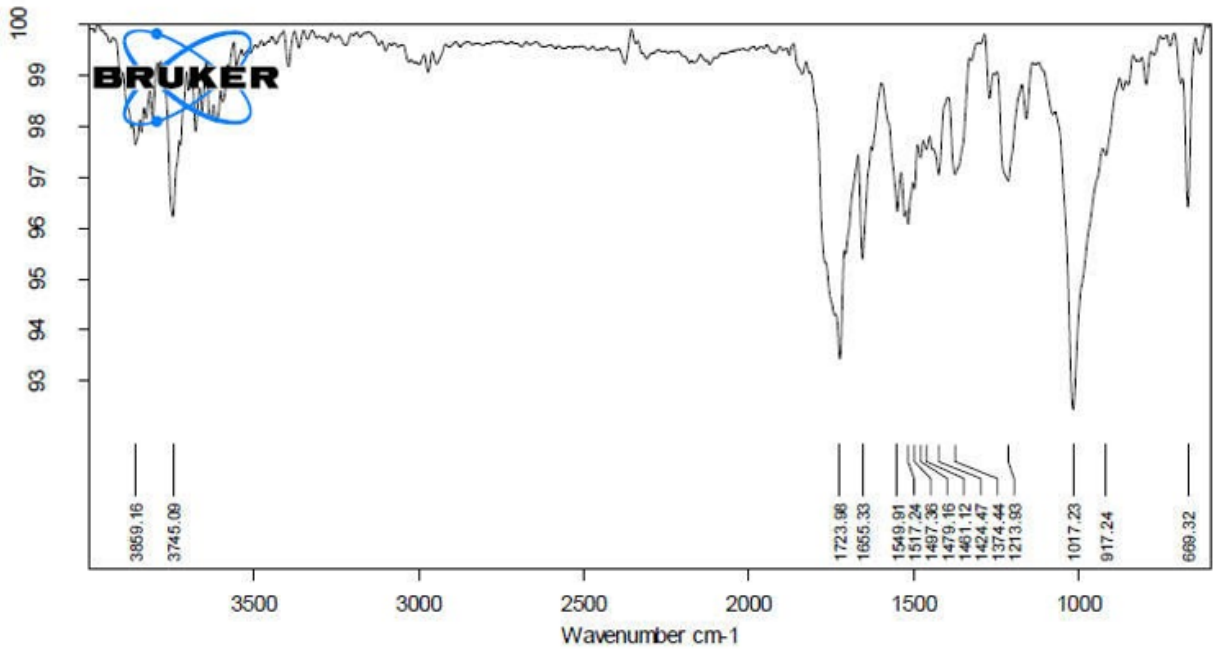

Figure 2: IR spectrum of Eplerenone with other excipients

Table 2: Drug Content & Entrapment efficiency Solid dispersion of Eplerenone

Formulation code	Drug Content (%)	% Entrapment efficacy
F1	62.20	69.14
F2	93.75	75.03
F3	93.60	82.63
F4	88.33	66.75
F5	93.25	70.81
F6	89.80	81.06

Table 3: *In-vitro* drug release of Eplerenone solid dispersions

Time (Min)	Percentage drug release					
	Eplerenone : HP β-Cyclodextrin			Eplerenone : β-Cyclodextrin		
	1:0.5(F1)	1:1(F2)	1:1.5(F3)	1:0.5(F4)	1:1(F5)	1:1.5(F6)
0	0	0	0	0	0	0
5	32.63	37.05	43.86	19.53	26.84	36.75
10	46.81	49.32	52.04	29.82	32.62	49.32
15	59.18	62.85	66.75	36.85	43.07	59.86
30	69.43	70.81	73.21	56.75	64.39	68.71
45	72.81	76.64	82.63	68.63	71.98	76.18
60	80.63	83.96	96.42	72.42	76.56	83.45

Table 4: Pre Compression parameters

Formulation	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±1.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±1.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±1.96	1.18±0.05

Table 5: Characterization Eplerenone Fast disintegrating tablets

Formulation	Weight variation	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegrating time (sec)	Drug content
F1	151.2±0.02	2.4±0.02	8.01±0.16	3.7±0.01	0.31±0.02	30.74±0.05	96.15±1.02
F2	149.3±0.06	2.5±0.04	8.03±0.04	4.1±0.03	0.03±0.06	27.68±0.03	97.75±0.54
F3	148.4±0.07	2.7±0.06	8.04±0.05	3.6±0.02	0.04±0.15	25.35±0.15	96.42±0.26
F4	151.6±0.04	2.4±0.01	8.06±0.75	3.8±0.01	0.16±0.05	29.52±0.04	94.63±0.64
F5	149.2±0.03	2.2±0.01	8.01±0.42	3.6±0.01	0.52±0.16	24.14±0.09	95.05±0.59
F6	149.8±0.02	2.5±0.02	8.02±0.16	4.0±0.06	0.14±0.32	20.16±0.04	98.96±0.22

Table 6: % Cumulative drug release of formulations F1-F6

Time(Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	30.15±0.04	36.38±0.10	44.19±0.42	29.53±0.14	35.15±0.88	46.05±0.14
10	43.41±0.12	52.25±0.44	61.06±0.12	38.42±0.52	49.52±0.62	58.26±0.26
15	56.25±0.35	60.56±0.26	84.05±0.28	49.16±0.38	68.21±0.54	70.53±0.14
20	70.38±0.26	76.74±0.12	90.36±0.14	61.52±0.51	73.63±0.82	88.18±0.22
30	82.75±0.24	92.15±0.54	97.36±0.14	76.23±0.22	84.72±0.35	95.06±0.36

Characterization of tablets

All official valuation variables like Hardness, Weight variation, Friability and drug content, Tablet thickness. The results are shown in the Table 5. Tablet hardness make in between 3.6 – 4.1kg/cm^2. Friability integrity have been < 1% all told acceptable. The % Drug content values of formulation F1 is 96.15%, F2 is 97.75%, F3 is 96.42%, F4 is 94.63%, F5 is 95.05%, F6 is 98.96%,.The drug content values for all the formulations found to be in the range of 94.63-97.75.The % Cumulative drug discharge of preparation F1 - F6 (Table 6 & Figure 3). Tablet drug release was explained with the help of mathematical model equations, i.e., zero-order and first-order methods. According to R^2 integrity of F3 obeys Zero-order kinetics.

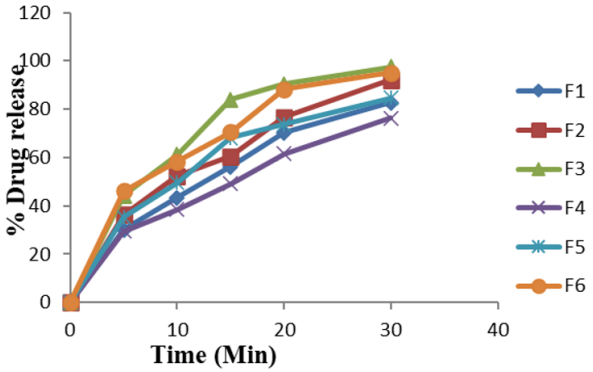

Figure 3: *In-vitro* drug release of formulations F1-F6

CONCLUSION

The HP β cyclodextrin and β cyclodextrin was used in the formulation of solid dispersions through solvent evaporation techniques. By observing the dissolution studies, the Eplerenone with HP β cyclodextrin (1:1.5) shows better drug release. And all the prepared solid dispersions were evaluated and results were explained in above mentioned data. From the customized formulation of the solid dispersions (i.e., F3) weight equivalent of Eplerenone was used along with the super disintegrants like SSG & crospovidone. The better drug release with Crospovidone (13.5mg) was 97.36% of drug waiver respectively end of 20 mins. Drug waiver mechanics of the optimized formulation shows Zero-order drug release.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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