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Research

Formulation and evaluation of eplerenone immediate release 25mg tablets

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Abstract

The present study aimed to improve the Solubility and Dissolution ratio of Eplerenone by preparation of Eplerenone nanosuspension by via nano-precipitation method. There is poor solubilities and slow dissolutions comparison are principal concerns for the edge of approaching drugs and presented biologically active combinations. Eplerenone is highly selective aldosterone blocker. It is treated for therapy of hypertension and heart failure, but question related with its poor solubility in biological solutions. Eplerenone is BCS Class-II having high permeability low and solubility. All the Eplerenone nanosuspension preparations were characterization for its Particle size and its distribution, Scanning Electron Microscopy, Zeta potential analysis, Drug excipient interactions investigated by using FT-IR examinations, Entrapment Efficiency (EE) and in vitro release kinetics. The adjusted formulation (Trail 6) showed an average particle size and zeta potential is 169.5.05 nm and -58 mV respectively. The dissolution profiling rate for the optimized nanosuspension was better relative to Eplerenone mainly due to the design of nanosized particles. Stability search discovered that nanosuspension was more stable at ambient room and cold condition with no significant change in particle size distribution. These effects indicate that the Eplerenone loaded Nanosuspension significantly increased in-vitro dissolution rate and thus probably enhance immediate start of therapeutic medication effect.

Keywords: Formulation, Evaluation, Eplerenone immediate release tablets, Solubility, Dissolution

INTRODUCTION

Eplerenone is classified as an aldosterone antagonist and has been available in the United States since 2002. Eplerenone key advantage over its older and less expensive drug in its class, spironolactone is its increased selectivity for the mineral corticoid receptor relative to glucocorticoid, progesterone, and androgen receptors. *Eplerenone is approved by the Food and Drug Administration (FDA) for:* The improvement of survival

of stable patients with left ventricular (LV) Systolic dysfunction (left ventricular ejection fraction less than or equal to 40")and congestive heart failure (CHF) after an acute myocardial infarction (MI).

Hypertension, alone or combined with other agents.Though the FDA specifies Eplerenone's use in heart failure specifically to those status- post myocardial infarction (EF) less than or equal to 35 percentage, especially when they have experienced an adverse effect to spironolactone. The use of Eplerenone in these populations has support from the EPHESUS and EMPHASIS – HF randomized controlled trials, respectively. Concerning its use in hypertension, Eplerenone is not a recommended agent for the initial treatment of hypertension. However, Eplerenone and spironolactone are preferred agents for patients with hypertension due to primary aldosteronism or resistant hypertension. Eplerenone has not been subject to prospective comparisons to spironolactone or other agents in head- to – head trials of resistant hypertension but may be used as an alternative to spironolactone, especially when a patient has experienced antiandrogen adverse effects from spironolactone.As an aldosterone antagonist, it is also used off- label to treat primary aldosteronism and ischemic heart disease. Eplerenone is used alone or in combination with other medications to treat high blood pressure. Eplerenone is in a class of medications called mineralocorticoid receptor antagonist. It works by blocking the action of aldosterone, natural substances in the body that raises blood pressures.

Eplerenone tablets contain Eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor. Eplerenone is chemically described as pregn-4-ene-7, 21-dicarboxylic acid, 9, 11-epoxy-17-hydroxy-3-oxo-, alpha-lactone, methyl ester, (7 alpha, 11alpha, 17 alpha)- its empirical formula is C24H30O6 and it has a Molecular weight of 414.50.

Immediate release formulation

Oral delivery of the pharmaceutical compositions of the present invention can include immediate release compositions as well as controlled release compositions. Preferably, the pharmaceutical compositions are in the form of immediate release tablets or capsules. The immediate release compositions comprise micronized Eplerenone in amount sufficient to provide the desired daily dosage of Eplerenone, that is, an amount of about 10mg to about 1000 mg, more preferably an amount of about 20mg to 400mg, still more preferably an amount of about 25mg to 200 mg, still more preferably an amount of about 25mg to 150mg, and still more preferably an amount of about 50mg to 100mg. A once-a-day immediate release tablets or capsules contains Eplerenone in an amount, for example, of about 50mg to about 100mg. Preferably, the same batch can be used to prepare tables (or capsules) of different strengths by compressing the formulation in different tablet sizes (or encapsulating the formulation in different capsule sizes or using different capsule fill weights). Although the amount of eplerenone in such novel compositions preferably discussed, the formulations also can be useful for the administration of an amount of eplerenone falling outside of the disclosed dosage ranges.

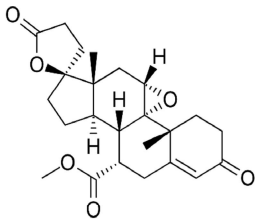
MATERIALS AND METHODS

Eplerenone, IH, Lactose monohydrate, USP, Micro crystalline cellulose, USP, Sodium Lauryl Sulphate, USP), Croscarmellose sodium, Hypromellose USP, Purified water, Talc USP, Magnesium stearate USP, Opadry Yellow, Vibratory Sifter, Rapid Mixture granulator 1000l, Fluid Bed Dryer, Multimill, Octagonal blender, Tablet compression Machine, Tablet deduster, Metal detector, Coating Machine, Analytical balance, Moisture analyzer, Bulk density apparatus, Vernier caliper.

Sr.No	Requirement	Raw material	Roles	Manufactures	Quantity per Unit in mg	Quantity per batch
1.	Eplerenone, IH	Active	Intra granular materials	DuPont Nutrition	25.000	15.000
2.	Lactose monohydrate, USP	Excipient	Intra granular materials	BASF Personal care and Nutrition Gmbh	36.465	21.879
3.	Micro crystalline cellulose, USP	Excipient	Intra granular materials	DuPont Nutrition	8.500	5.100
4.	Sodium Lauryl Sulphate, USP-)	Solvent	Intra granular materials	Dow Chemical International Pvt. Ltd	0.085	0.051
5.	Croscarmellose sodium,	Excipient	Intra granular materials	BASF Personal care and DuPont Nutrition NutritionGmbh	4.250	2.550
6.	Hypromellose USP	Excipient	Granulation:	DuPont Nutrition	0.850	0.510

Sr.No	Requirement	Raw material	Roles	Manufactures	Quantity per Unit in mg	Quantity per batch
7.	Purified water	Solvent	Granulation:	Inhouse/USP/EP	0.850	0.510
8.	Croscarmellose sodium, USP)	Excipient	Pre-Lubrication	BASF Personal care and Nutrition Gmbh	0.850	0.510
9.	Micro crystalline cellulose	Excipient	Pre-Lubrication	DuPont Nutrition	0.850	0.510
10.	Talc USP	Excipient	Pre-Lubrication	Imerys Talc Italy S.p.A	0.850	0.510
11.	Magnesium stearate, USP	Excipient	**Lubrication:**	Peter Greven	14.450	14.450
12.	Opadry Yellow	Excipient	Coating	Colorcon	2.550	1.989
13.	Purified water,	Excipient	Coating	Inhouse/USP/EP	14.450	11.271

Drug profile: eplerenone



- Generic Name: Eplerenone
- Drug Class: Mineralocorticoid Receptor Antagonist (Selective Aldosterone Blocker)
- Dosage Form: Tablet
- Strength: 25 mg
- Mechanism of Action:
- Eplerenone is a selective aldosterone receptor antagonist. Aldosterone is a hormone that increases sodium reabsorption and potassium excretion in the kidneys. By blocking aldosterone receptors, eplerenone reduces sodium reabsorption and promotes the excretion of sodium and water, which helps to lower blood pressure and reduce fluid retention. This mechanism also spares potassium, reducing the risk of hypokalemia (low potassium levels).

Indications

- Heart Failure Post-Myocardial Infarction: Eplerenone is used to improve survival in patients who have heart failure with reduced ejection fraction (HFrEF) following a myocardial infarction.
- Hypertension: Eplerenone is indicated for the treatment of hypertension to lower blood pressure. Lowering blood pressure helps to reduce the risk of strokes, heart attacks, and kidney problems.

Representation of the in process test during the formulation and manufacturing of the product

Sr.No	Test	Methods
Granulation :		
1.	Loss of Drying	Performed in moisture analyzer balance
2.	Bulk density	Measurement of Bulk density was done by pouring powder into a measuring cylinder through sieve # 20 and the initial weight was noted. The initial volume was termed as bulk volume.11
3.	Tapped density	Tapped density is defined as the ratio between aggregate weights of granules to the tapped volume of powder. Measurement of the volume was done by tapping the granules 750 times. If the variance in volume exceeds 2%, further tapping should be done for 1250 times. It was conveyed in g/ml
4.	Angle of Repose	Angle of repose was done by using powder flow tester. Angle of repose can be calculated by measuring the height and radius of the pile of granules
5.	Compressibility index	It demonstrates the flow properties of the granules. It is conveyed in the form of % and can be calculated using bulk density and tapped density.

Sr.No	Test	Methods
6.	Hausner Ratio	Hausner ratio is an indirect way of accessing the ease of granules flow. It can be calculated by using bulk density and tapped density
Compression		
7.	Weight Variation	Randomly 20 tablets were selected and weighed using a single balance. Standard deviations were calculated and checked with the standard pharmacopeial limits.
8.	Thickness	Tablets were selected randomly from all batches and measurement of thickness was done by using Vernier Calliper.1
9.	Hardness	The strength of tablet is expressed in the form of tensile strength (Kg/cm2). The amount of force required to break the tablets was measured by using a hardness tester
10.	Friability	Randomly 20 tablets were selected and weighed from all the batches. The weighed tablets then placed in friabilator and then ran for 100 revolutions. After completion of 100 revolutions tablets were de-dusted, re-weighed and %friability was calculated.

Based on the results of studies it concluded that the selected excipient are compatible with active pharmaceutical ingredient Eplerenone . With 60ºC open and closed condition API and propylene glycol related substances are failing with respect to limit, but it is compiled with active pharmaceutical ingredient and placebo combination study. Hence it confirms the compatibility.

Manufacturing Process

Unit Parameter	Process Parameter	Quality Attributes
Dry Mixing	Order of addition	Particle size distribution , Bulk/tapped density ,flow properties
	RMG amperage	
	Impeller Speed and time	
	Mixing	
Wet Granulations	Binder addition time	Granules size, Granule shape, flow properties
	Impeller Speed	
	Chopper Speed and Run time	
	Binder fluid temperature	
	Post granulation fix time	
Milling	Speed of mill	Blend Uniformity flow, Particle size and distribution, Granules size and distribution, granules strength and uniformity solid form
	Screen size	
	Feeding rate	
Drying	Inlet temperature, inlet air flow, volume	Granule size and distribution , granules strength and uniformity,
	Bowl temperature	
	Exhaust temperature	

Manufacturing Process Experimental Designed for the formulation

Table 1: Different quantity of ingredient were change for the formulation to optimized the formula

Ingredient	Quantity in batch per kg (mg/Tablets)						
	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6 %w/w	Quantity/ Unit(mg)
Intra Granular Material:							
Eplerenone, IH	25	25	25	25	25	29.41	25.000
Lactose monohydrate, USP	34	34	36.7	36.253	36.465	42.90	36.465
Micro crystalline cellulose, USP	8	7	8.445	8.7	8.5	10.00	8.500
Sodium Lauryl Sulphate, USP-	0.085	0.085	0.075	0.085	0.085	0.10	0.085
Croscarmellose sodium,	7.215	8.215	4.08	4.25	4.25	5.00	4.250
						87.41	74.3
Granulation:							
Hypromellose USP	2.550	2.550	2.550	2.550	2.550	3.00	2.550

Table 1: Different quantity of ingredient were change for the formulation to optimized the formula							
Ingredient	**Quantity in batch per kg (mg/Tablets)**						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6 %w/w**	**Quantity/ Unit(mg)**
Purified water	22.290	22.290	22.290	22.290	22.290	---	22.290
Croscarmellose sodium, USP)	14.860	14.860	14.860	14.860	14.860	---	14.860
Extra Granular Materials							
Croscarmellose sodium, USP	1.700	1.700	1.700	1.700	1.700	2.00	1.700
Micro crystalline cellulose, USP	5.175	5.175	5.175	5.175	5.175	6.09	5.175
Talc USP	0.850	0.850	0.850	0.850	0.850	1.00	0.850
Lubrication:							
Magnesium stearate,	0.425	0.425	0.425	0.425	0.425	0.50	0.425
Core Tablet weight						**100.00**	**85.000**
Coating							
Opadry Yellow	1.989	1.989	1.989	1.989	1.989	2.550	1.989
Purified water, IHS/USP/Ph.Eur@	11.271	11.271	11.271	11.271	11.271	14.450	11.271
Total	**87.550**	**87.550**	**87.550**	**87.550**	**87.550**	**87.550**	**87.550**
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent

From the above table all in process control and parameter is observed well within criteria for Trail batches Trail 6.

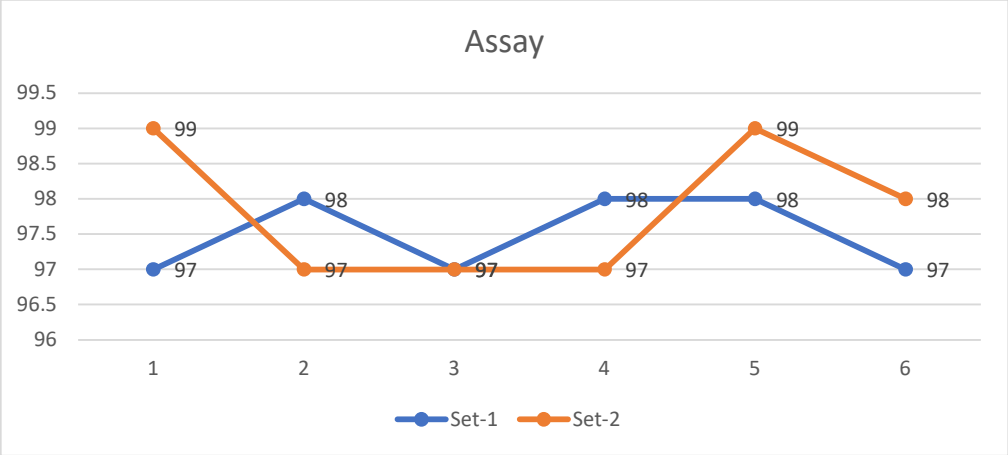
The samples were collected for the testing of Physical parameters, Uniformity of Dosage unit's test and Dissolution test (At optimum speed), the obtained results are summarized in below tables.

Compression Inprocess checks

PARAMETER	**SPECIFICATION**
Description	White to off white, round, biconvex tablets de-bossed with "V" on one side and "68" on the other side.
Weight of 10 tablets (g) ^	0.850 g± 4.0 % (0.816 g– 0.884 g)
Weight of individual tablets (mg)	85 mg ± 5.0 % (80.75 mg – 89.25 mg)
Friability (%w/w)	NMT 1.0 %w/w
Thickness (mm) ^	3.0 mm ± 0.3 (2.7 mm – 3.3 mm)
Hardness (Kp) ^	8.0 Kp (4.0 Kp – 12 .0 Kp)
Disintegration time (min)	NMT 15 minutes
Compression machine Speed (RPM)	PM) 10 – 70 RPM

Summary of analytical results (Assay of Tablets)

Assay	**Trail 6**	**Trail 6**
1	97	99
2	98	97
3	97	97
4	98	97
5	98	99
6	97	98
Minimum	**97**	**97**
Maximum	**98**	**99**
Average	**97**	**98**
HPLC	QC-HPLC001	QC-HPLC001
Column	QC-COL-003	QC-COL-002



Uniformity of dosage units of Tablets

Test	Acceptance criteria	Trail6			
		Sample ID	**Set-1**	**Set-2**	**Set-3**
Uniformity of dosage units (By weight Variation) (USP<905 & In-House) Acceptance Value (L1)	Not more than 15.0.	Tablet -1	97.06	98.00	99.75
		Tablet -2	99.37	97.83	98.99
		Tablet -3	97.91	96.75	98.64
		Tablet -4	98.57	98.80	98.12
		Tablet -5	97.79	96.85	97.40
		Tablet -6	97.71	99.41	97.80
		Tablet -7	97.05	97.57	96.88
		Tablet -8	98.36	97.32	96.62
		Tablet -9	97.85	98.79	97.85
		Tablet -10	97.33	97.69	96.96
		Acceptance Value	**2.3**	**2.7**	**3.0**
		Mean	**97.9**	**97.9**	**97.9**
		SD	**0.72**	**0.87**	**1.00**

S. No.	Acceptance Criteria	Trail 6				
		10 Minutes	**15 Minutes**	**20 Minutes**	**30 Minutes**	**45 Minutes**
1	For Information (%)	94	95	97	97	97
2		93	94	95	96	96
3		91	96	97	98	97
4		94	98	97	98	98
5		90	95	96	96	96
6		86	97	97	98	98
7		86	93	94	95	95
8		86	96	96	96	97
9		85	94	94	95	95
10		92	95	97	96	97
11		82	92	95	95	96
12		91	95	96	96	96
Minimum		**82**	**92**	**94**	**95**	**95**
Maximum		**94**	**98**	**97**	**98**	**98**
Average		**89**	**95**	**96**	**96**	**97**
% RSD		**4.5**	**1.7**	**1.2**	**1.2**	**1.0**

Sample was collected for the testing of dissolution profile as per the sampling plan of process validation protocol and the results were found satisfactory.

SUMMARY AND CONCLUSION

Qualified Facilities, Utilities and Equipments used for manufacturing process. Analytical methods used for testing are validated.Operational/process parameters at various stages are evaluated against the predetermined specifications and criteria as per batch records Based on summary, the limits proposed/recommended (refer section 'Recommendations'). At Compression stage, during compression, at optimum speed samples were collected as per sampling plan of protocol and evaluated for Tablet physical parameters, Dissolution and Uniformity of dosage unit (UOD). All the results were found well within the predetermined specifications and quality attributes.

The current research work predicts the applicability of QbD in manufacturing Eplerenone The solid dispersions methodology is the most practical and least expensive method to increase the solubility and dissolution rate of poorly water-soluble eplerenone. Formulating lipid-based solid dispersions employing a mix of hydrophilic lipid carriers has shown to be quite common. From the outcomes it was clearly apparent that as the polymer concentration increases, there was a decline in the release of drug. Grouping of polymers with other excipients do not interact with drug and vice versa, which informations to sustained delivery of drug for longer periods. Eplerenone is better absorbed and transported with the help of formulation Trail 6. To investigate permeability further, ex vivo tests were undertaken with impressive results compared to what was available on the market.

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