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RESEARCH ARTICLE

SOLUBILITY AND DISSOLUTION ENHANCEMENT OF EPLERENONE BY USING NANOPRECIPITATION TECHNIQUE

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ABSTRACT

The present study aimed to increase the Solubility and Dissolution rate of Eplerenone by formulation of Eplerenone nanosuspension by using nanoprecipitation technique. Poor solubility and slow dissolution rate are major issues for the majority of upcoming drugs and existing biologically active compounds. Eplerenone is highly selective aldosterone blocker. It is used for treatment of hypertension and heart failure, but problem associated with its poor solubility in biological fluids. Eplerenone is BCS Class-II having low solubility and high permeability. All the Eplerenone nanosuspension formulations (F1 to F12) were characterization for its Particle size and its distribution, Zeta potential analysis, Scanning Electron Microscopy, Drug excipients interactions investigated by using FT-IR examinations, Entrapment Efficiency (EE) and in vitro release kinetics. The optimized formulation (F12) showed an average particle size and zeta potential is 179.05 nm and -55 mV respectively. The dissolution rate for the optimized nanosuspension was enhanced (97.05 % in 45 min) relative to pure Eplerenone (30 % in 60 min), mainly due to the formulation of nanosized particles. Stability study revealed that nanosuspension was more stable at room and refrigerator condition with no significant change in particle size distribution. These results indicate that the Eplerenone loaded Nanosuspension significantly improved in-vitro dissolution rate and thus possibly enhance fast onset of therapeutic drug effect.

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INTRODUCTION

Oral route is the most common and popular route for administration of drugs (Gupta, 2009). More than 40% of the new chemically synthesized drugs being generated through drug discovery programmers are poorly water soluble or lipophilic compounds (BCS in class II and IV) (Savjani, 2012). The uptake of poorly soluble drugs cannot be completed within the time at absorption site due to slow dissolution rate and generation of a low concentration gradient across the gastrointestinal tract leading to possibilities of gastric decomposition of drug due to longer gastrointestinal residence time and low bioavailability (Kumar, 2013). This type of drugs has always been a challenging problem to pharmaceutical scientists in formulating suitable dosage forms (Vuppalapati, 2016). The major challenge of current pharmaceutical research is to enhance the solubility, dissolution, absorption efficiency and bioavailability of insoluble drugs.

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Therapeutic effectiveness of a drug depends upon the bioavailability which in turn dependent on the solubility and dissolution rate of drug. The dissolution rate is often the rate determining step in the absorption of lipophilic or water insoluble drugs which belong to BCS class II drugs (Kulkarni, 2010). Eplerenone is 9α, 11-Epoxy-7α-methoxycarbonyl-3-oxo-17 α- Pregn-4-ene-21,17-carbolactone (Indian Pharmacopoeia, 2014). Eplerenone is the first highly selective aldosterone receptor antagonist to effectively block aldosterone at receptor sites in body tissues, aldosterone being a component of rennin angiotensin aldosterone system and it is used for treatment of hypertension and heart failure (Brajesh, 2011; Moore, 2003). Nanosuspension is one of the most important strategies to enhance the oral bioavailability of poorly water soluble drugs (Desai, 2012). Now a day's preparing nanosuspension can be a challenging technique. Various methods which are generally used to prepare nanosuspension are bottom-up including precipitation and top-down including media milling, emulsion solvent diffusion method, supercritical fluid method, dry co-grinding, high-pressure homogenization, Nano edge (Lakshmi, 2010; Suman,

2009). Nanosuspension have two particular advantageous properties, firstly increased saturation solubility and secondly the enlarged surface. Both properties results in an increase in the dissolution rate according to the Noyes and Whitney Law (Noyes, 1897). In general it is advantageous to use nanoparticles that are as small as possible to achieve a maximum improvement in the oral bioavailability or a very rapid dissolution rate (Salazar, 2012; Ghosh, 2012).

MATERIALS AND METHODS

MATERIALS

The drug Eplerenone was purchased from BMR Pharma & Chemical Suppliers, Hyderabad, Telangana, India. Poloxamer 407, PVP K30, and Sodium Lauryl Sulphate (SLS) were purchased from BMR Pharma & Chemical Suppliers, Hyderabad, Telangana, India. Methanol and other chemicals were (Loba Chemie Pvt Ltd, Mumbai, Maharashtra, India) obtained commercially and used as such.

METHODS

Eplerenone calibration curve: Eplerenone calibration curve was prepared by using pH 6.8 phosphate buffer in the concentration range of 2-12 µg/mL and they were analyzed spectrophotometrically (UV-Visible Double Beam Spectrophotometer) at 244 nm. The regression coefficient is 0.999 and graphically represented was shown in Figure I.

Preparation of Eplerenone Nanosuspensions: Nanosuspensions were prepared by using a nanoprecipitation method. The Pure drug Eplerenone was dissolved in (1 mL) Methanol at 45^0C to form uniform organic solution. The prepared organic solution was then injected slowly drop wise with the help of a syringe into an aqueous phase (20 mL) containing stabilizer (poloxamer 407) under high speed mechanical agitation of 7000 rpm to get desired nanodispersion. Prepared nanosuspension was then stirred magnetically at 500 rpm at room temperature for 12 hr to evaporate organic solvent. Complete evaporation of methanol was determined by spectrophotometric method. The volume was then adjusted with the addition of triple distilled water to recover loss in keeping other parameters constant (15). All the formulations were prepared according to design the composition of Eplerenone Nanosuspensions and show in Table No.1.

CHARACTERIZATION OF NANOSUSPENSIONS

Solubility study of Eplerenone: Solubility study of Eplerenone was determined by using 0.1N HCL, ethanol, methanol, pH 6.8 and pH 7.4 phosphate buffers. Solubility study was performed by taking excess amount of Eplerenone in beakers containing the above solvents. The mixtures were shaken for 24 hours and the solutions were filtered by using whatman filter paper grade No: 41. The filtered solutions were analyzed spectrophotometrically. The solubility data of Eplerenone and its graphically represented were shown in Table No.3 and Figure VIII respectively. The solubility study was observed that methanol has more solubility than the other organic solvents. The percentage solubility of methanol is 4.21±0.08%, further it is used for formulations of Nano suspensions.

Zeta potential and particle size analysis: The zeta potential, particle size and its distribution of Eplerenone nanosuspensions were determined by using Malvern Zetasizer ZS (Microtrac Inc., USA). Zetatrac utilizes a high frequency AC electric field to oscillate the charged particles. The Brownian motion power spectrum was analyzed with modulated power spectrum technique, a component of power spectrum resulting from oscillating particles. Nanocrystals equivalent to 100 mg of sample were suspended with sufficient water, samples were directly placed into cuvette and particle size as well as zeta potential were measured.

Scanning Electron Microscopy (SEM): The morphological features of Eplerenone nanosuspensions are observed by using scanning electron microscope at different magnifications.

Drug Excipients interaction studies: Pre-formulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, binders, stabilizers, solvents and lubricants used in formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned.

Therefore, in the present studies Eplerenone, PVP K30, SLS, Poloxamer 407 and excipients were used and analyzed for compatibility studies. Present investigation fourier transform infrared spectroscopy (Perkin-Elmer series 1615 FTIR Spectrometer) was used to determine any possible interactions between the Eplerenone, Polymers and excipients which were used in preparation of Nanosuspensions.

Determination of EE of nanosuspension: Freshly prepared 10 mL of nanosuspension was centrifuged at 7000 rpm for 30 min at 5^0c temperature. The supernatant solution was filtered and separated 2 mL of this filtrate was diluted with water and the absorbance at maximum wavelength (λmax) was measured by UV spectrophotometer against water as a blank. The amount of free drug in the formulations was measured and the entrapment efficiency is then calculated from Eq.1 the results were analyzed in triplicate and standard deviations are reported.

$$E = \frac{(T \quad d \quad in \ f(\quad - F \quad d \quad)}{T \quad d \quad in \ f(} x1$$

In vitro release kinetics: The In-vitro dissolution studies of all the formulations (F1 to F12) were evaluated by using USP dissolution apparatus Type-II and the medium was used for 900 mL of pH 6.8 phosphate buffer.

The temperature should be maintained at 37 ± 0.5°C with paddle stirred at 50 rpm and 5 mL of sample was withdrawn at different time intervals, then filtered through 0.45µm filter paper & at the same time an equivalent volume of medium (5 mL) was replaced on it, to maintain sink condition. The samples were analyzed by UV Visible double beam spectrophotometer (Model: T60 UV) at 244 nm.

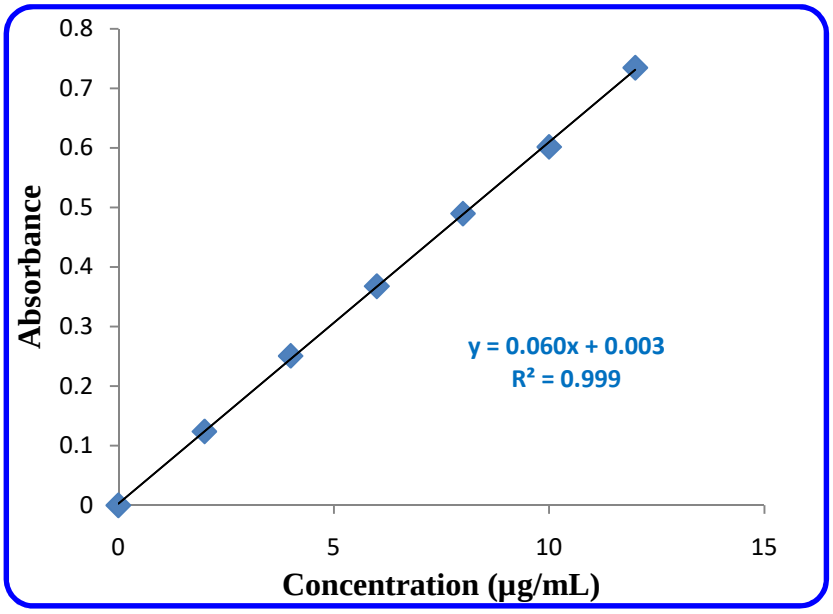

Figure I: Calibration curve of Eplerenone

Table No: 1: Composition of Eplerenone Nanosuspension

S. No	INGREDIENTS (mg/mL)	FORMULATIONS WITH CODE											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Eplerenone	200	200	200	200	200	200	200	200	200	200	200	200
2	PVP K30	10	20	30	--	--	--	10	20	30	--	--	--
3	Poloxamer 407	--	--	--	10	20	30	--	--	--	10	20	30
4	SLS	5	5	5	5	5	5	10	10	10	10	10	10
5	Methanol (mL)	3	3	3	3	3	3	3	3	3	3	3	3
6	Water (mL)	40	40	40	40	40	40	40	40	40	40	40	40

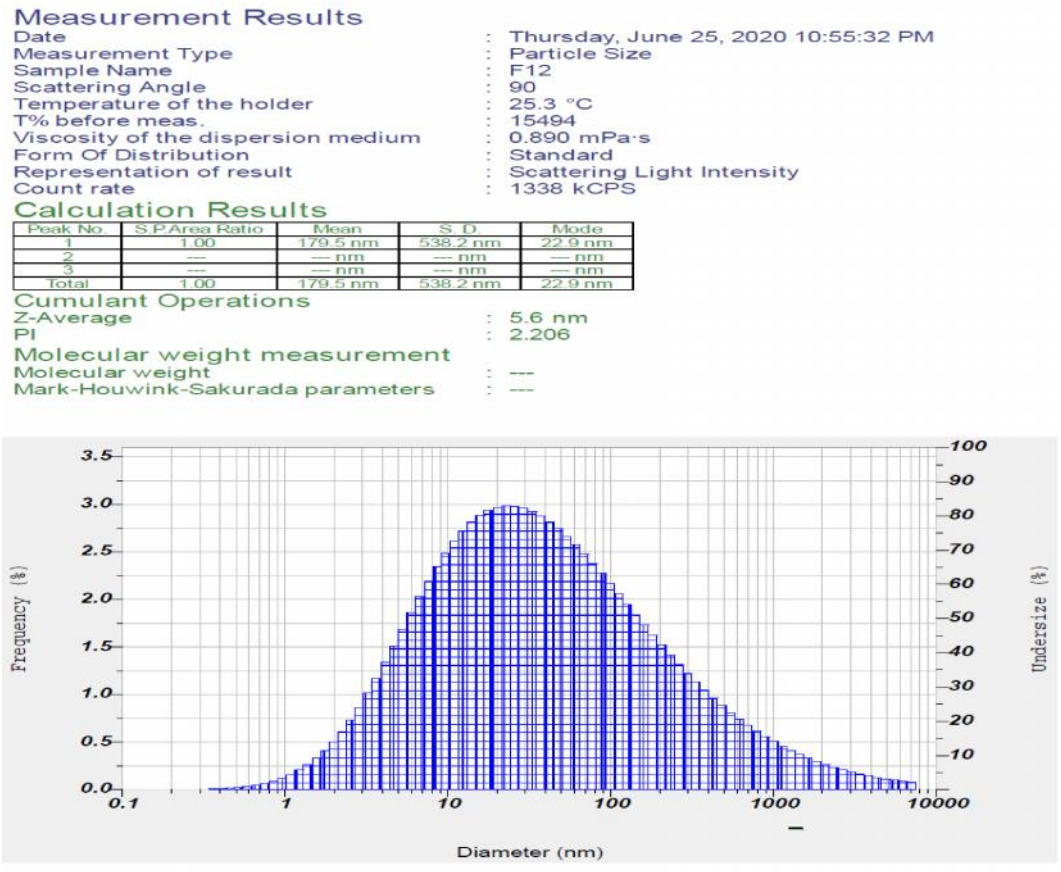

Figure II. Particle size analysis for optimized formulations (F12)

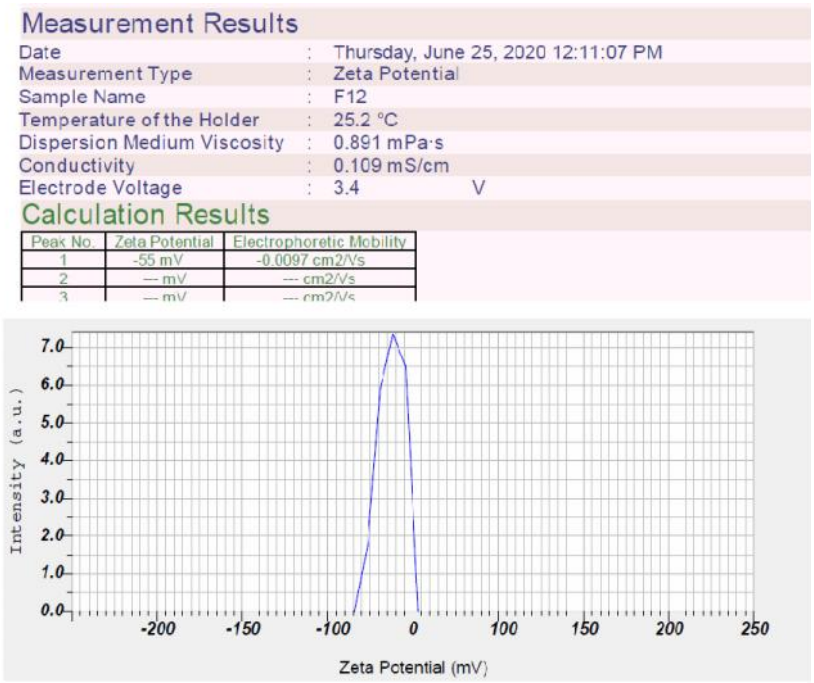

Figure III. Zeta potential for optimized formulation (F12)

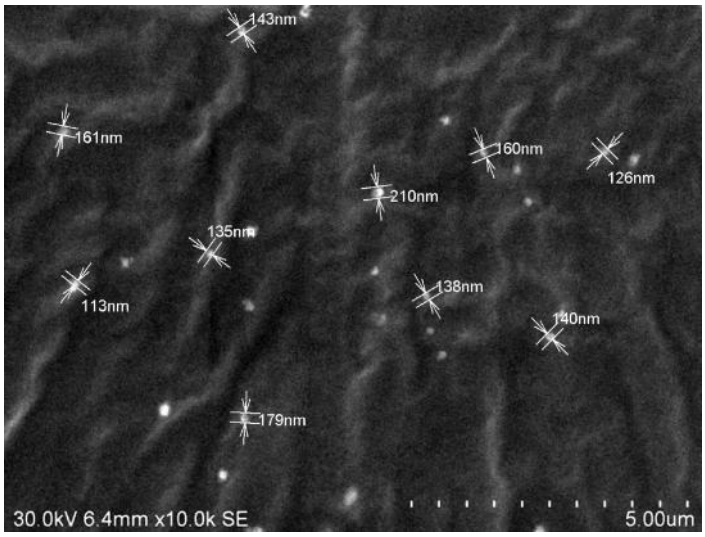

Figure IV. SEM image of Eplerenone Nanosuspension

Table No.2. Physicochemical characterization of Eplerenone Nanosuspension

S. No	FORMULATIONS	Particle size (nm)	Polydispersity Index	Zeta potential (mV)	Percentage of EE
1	F1	143±0.22	0.358±0.15	-45±0.89	92.53±0.21
2	F2	161±0.29	0.487±0.54	-42±0.66	90.46±0.15
3	F3	160±0.53	0.561±0.32	-54±0.85	95.36±0.62
4	F4	126±0.47	0.421±0.94	-47±0.77	92.05±0.74
5	F5	210±0.18	0.456±0.55	-47±0.58	91.05±0.21
6	F6	135±0.29	0.558±0.17	-48±0.89	85.36±0.34
7	F7	113±0.25	0.345±0.12	-53±0.79	95.31±0.19
8	F8	138±0.41	0.389±0.98	-51±0.82	92.76±0.58
9	F9	140±0.49	0.487±0.34	-53±0.56	90.53±0.68
10	F10	135±0.29	0.398±0.54	-48±0.25	93.15±0.72
11	F11	167±0.23	0.359±0.89	-47±0.24	90.54±0.81
12	F12	179±0.27	0.307±0.08	-55±0.09	96.34±0.11

All the values are expressed in Mean± SD, N=3

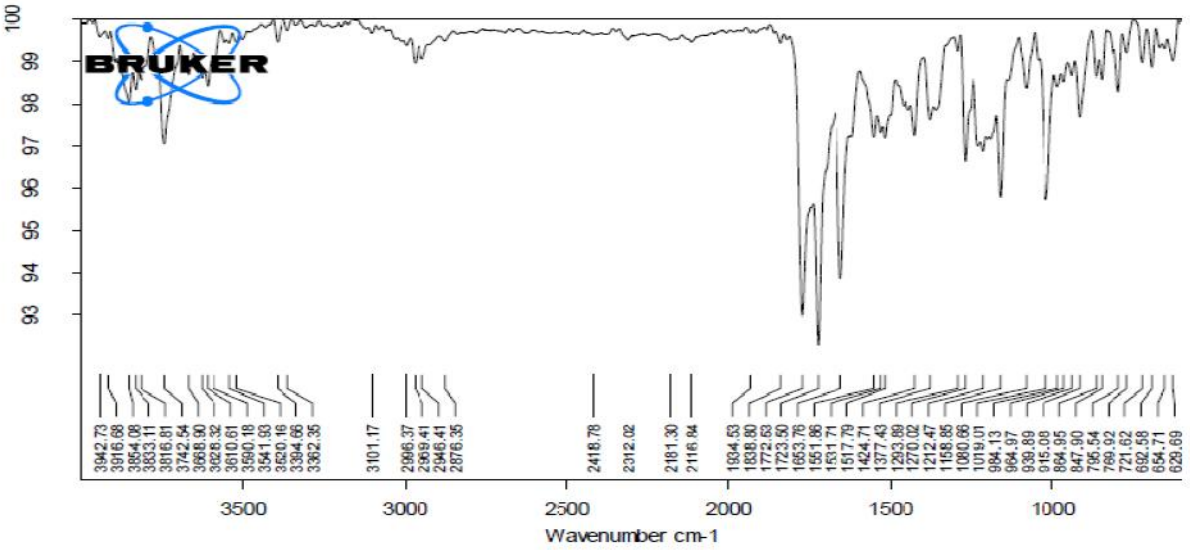

Figure V: FTIR Spectrum of pure Eplerenone

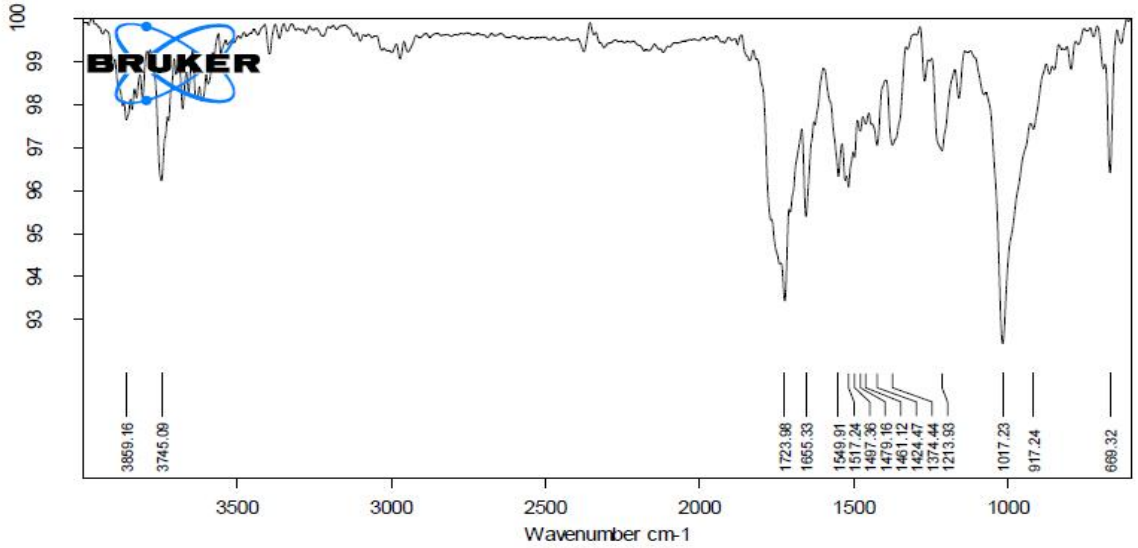

Figure VI: FTIR Spectrum of Eplerenone optimised formulation (F12)

Table No 3. Solubility studies of Eplerenone

S. No	Name of Solvents	Percentage of Solubility
1	0.1N HCL	0.985±0.67
2	Ethanol	3.46±0.52
3	Methanol	4.21±0.08
4	pH 6.8 Phosphate Buffer	1.235±0.24
5	pH 7.4 Phosphate Buffer	1.024±0.58

All the values are expressed in Mean± SD, N=3

RESULTS AND DISCUSSION

Nanoprecipitation method has been employed to produce nanosuspension of Eplerenone. Eplerenone is a BCS Class-II drug having low solubility and high permeability. Drug and stabilizer ratio was contributed much towards the change in particle size in nanosuspension formulation. Dissolution rate and saturation solubility of poorly soluble drug of Eplerenone has been enhanced due to reduction of particle size diameter down to the submicron range. Nanosuspension of Eplerenone was prepared as per composition shown in Table No.1.

Particle size and Polydispersity Index: The particle size distribution has most important characteristics affecting the in vivo fate of nanosuspension. The average particle sizes of all the formulations (F1-F12) were observed from the ranges of 113 to 210 nm and shown in Table No.2. The largest size 2100 nm in F1 batch which could be due to the lower concentration of stabilizer, because too little concentration of stabilizer induces agglomeration or aggregation and too much concentration promotes ostwald ripening. The optimized formulation (F12) showed an average particle size is 179.5 nm and shown in Figure II.

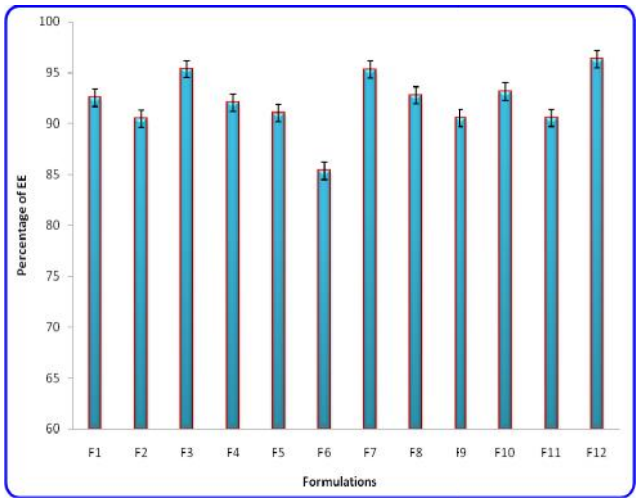

Figure VII: Eplerenone EE of All the Nanosuspensions (F1 to F12)

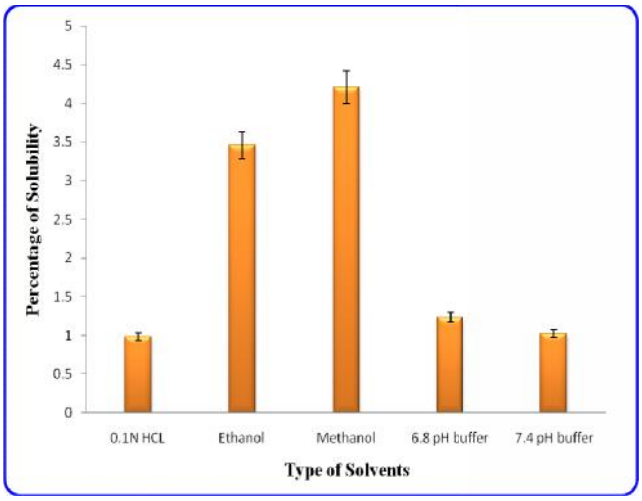

Figure VIII. Solubility studies of Eplerenone

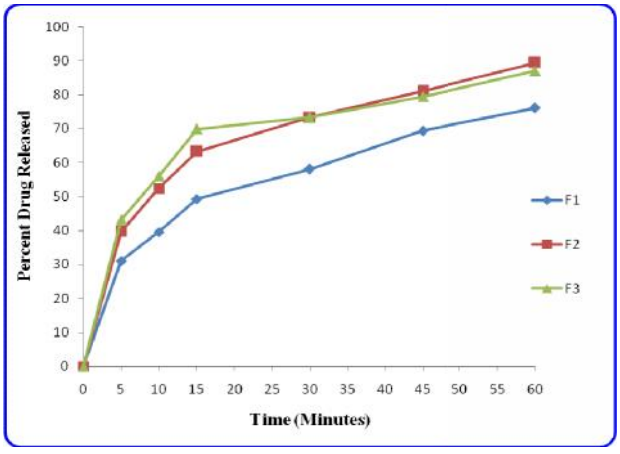

Figure IX: Eplerenone released profiles of F1 to F3

Zeta potential analysis: The Zeta potential governs the degree of repulsion between adjacent or similarly charge of dispersed particles. It is an important parameter for prediction of stability of nanosuspension. All the formulations (F1 to F12) Zeta potential was observed between -42 mV to -55 mV and show in Table No.2. Zeta potential of optimized formulation (F12) was found to be -55 mV and shown in Figure III. Thus, it was concluded that the system had sufficient stability.

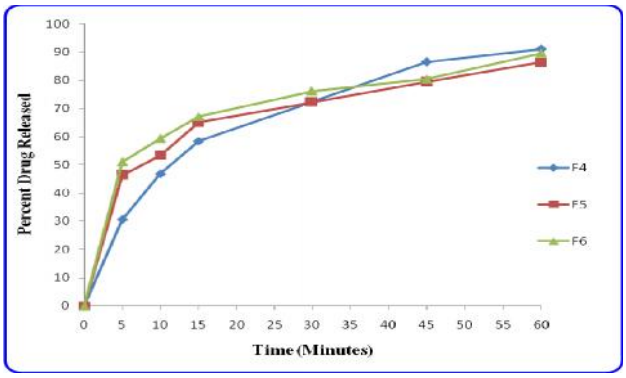

Figure X: Eplerenone released profiles of F4 to F6

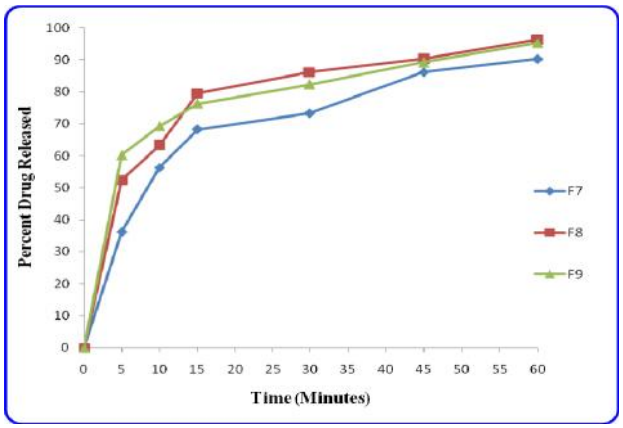

Figure XI. Eplerenone released profiles of F7 to F9

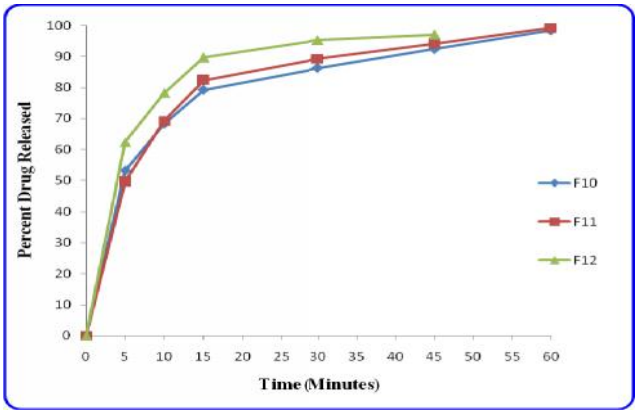

Figure XII. Eplerenone released profiles of F10 to F12

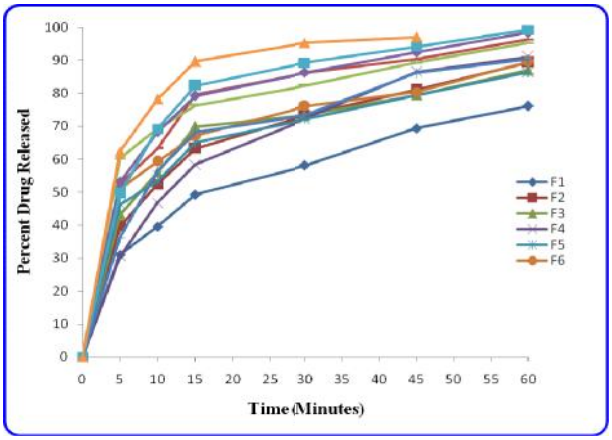

Figure XIII: Comparison the Eplerenone released profiles of F1 to F12

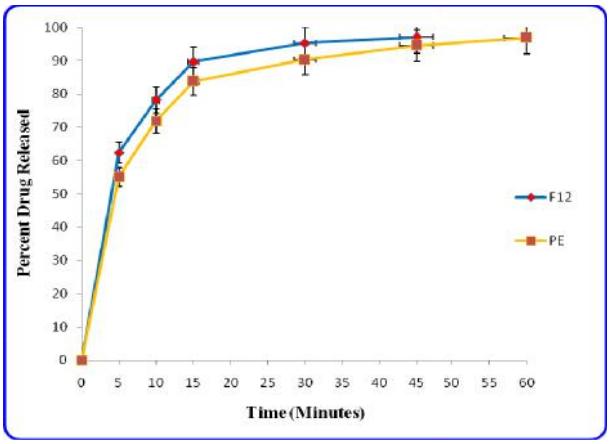

Figure XIV. Comparison the in vitro release of optimized formulations (F12) with Pure Eplerenone (PE)

Scanning electron microscopy: The morphological features of Eplerenone nanosuspensions were observed by scanning electron microscope at different magnifications image as shown in Figure IV.

Drug interaction studies by FT-IR: FT-IR spectroscopic studies were conducted to determine possible interactions between drug and excipients. IR spectra of Eplerenone with PVP K30, Poloxamer 407, SLS. This shows no chemical interaction between Eplerenone and excipients. The FTIR spectrums of pure Eplerenone and optimised formulation (F12) were show in Figure V & VI respectively.

Solubility Study: The saturation solubility of Eplerenone was increase due to the particle size reduction and subsequent increase in surface area. This great increase in saturation solubility of Eplerenone due to particle size reduction can be attributed to enhanced dissolution and increase the bioavailability of drug was justified the objective of research work. The solubility study of Eplerenone data and it's graphically represented were show in Table No.3 & Figure VIII.

In-vitro drug release: The most important feature of nanoparticles is the increase in the dissolution velocity, not only because of increase in surface area but also increase in saturation solubility. In-vitro drug release data from the nanosuspension were carried out for 60 min and graphically represented as percentage drug release versus time profiles were show in Figure IX to XIII. The percentage drug release curve of formulation F12 and pure drug showed the desired rate in phosphate buffer of pH 6.8 up to 60 min. From that study it was found that formulation of F12 batch gave the faster release behaviour compared to pure drug of Eplerenone. The drug release of optimized formulation (F12) was found to be 97.05% within 45 min. Thus, from the above results it was found that as the particle size is decrease drug release is increased. So, nanosuspension technique was enhanced rate of dissolution of Eplerenone to a great extent.

Conclusion

Nanoprecipitation method was successfully used to produce stable Eplerenone nanosuspension which can enhance the solubility and dissolution rate. In this process, the particle size of Eplerenone can be obtained in the nano size ranges by adjusting the operation parameters such as surfactant concentration, polymer concentration and agitation speed (7000 rpm) was constant. From the above investigation, it is concluded that the drug to stabilizer ratio (1:20) and drug to polymer ratio showed a pronounced effect on particle size reduction. According to optimized batch (F12) the mean particle size and zeta potential were found to be 179.5 nm and -55 mV respectively and stable at various conditions. The rate of dissolution of the optimized nanosuspension was enhanced by 97.05% in 45 min and follows first order release kinetics, relatively to pure Eplerenone (30% in 60 min). This improvement of dissolution rate was mainly due to formation of nanosized particles. Thus, Eplerenone nanosuspension formulation prepared by nanoprecipitation method may be therapeutically superior to conventional formulations. The dissolution rate of the nanosuspension significantly enhances as compared with the pure drug.

REFERENCES

Brajesh M, Naina K and Shashank S. Quantitative determination of Eplerenone in bulk drug and tablet dosage form by TLC/densitometry. Int J Pharm Life Sci. 2011: 2 :502-505.

Desai PP, Date AA and Patravale VB. Overcoming poor oral bioavailability using nanoparticle formulations opportunities and limitations. Drug Discov Today Technol. 2012: 9(2): e71–174.

Fessi H, Puisieux F, Devissaguet JP, Ammoury N and Benita S. Nanocapsules formation by interfacial polymer deposition following solvente displacement. Int J Pharm, 1989: 55: R1-R4.

Ghosh I, Schenck D, Bose S, and Ruegger C. Optimization of formulation and process parameters for the production of nanosuspension by wet media milling technique: Effect of vitamin E TPGS and nanocrystal particle size on oral absorption. Eur J Pharm Sci. 2012: 47(4): 718-728.

Gupta H, Bhandari D, and Sharma A. Recent trends in oral drug delivery: A Review. Recent patents on drug delivery and formulation. 2009: 3(2): 162-73.

Indian Pharmacopoeia, Ministry of Health and Family Welfare, Indian Pharmacopoeia Commission, Ghaziabad, 2014, 1958.

Kulkarni AS, Aloorkar NH, Mane MS and Gaja JB. Liquisolid systems: A Review. International Journal of Pharmaceutics and Nanotechnology. 2010: 3(1): 795-803.

Kumar P and Singh C. A study on solubility enhancement methods for poorly water soluble drugs. American Journal of Pharmacological Sciences. 2013: 1(4): 67-73.

Lakshmi P and Kumar G.A. Nano suspension technology: a review. Int J Pharm Pharm Sci 2010; 2(4):35-40.

Moore TD, Nawarskas JJ, and Anderson JR. Eplerenone: a selective aldosterone receptor antagonist for hypertension and heart failure. Heart Dis. 2003: 5: 354-363.

Noyes AS and Whitney WR. The rate of solution of solid substances in their own solutions. J. Am .Chem. Soc. 19,930, 1897: 19,12: 930-934.

Salazar J, Ghanem A, Müller RH and Moschwitzer JP. Nanocrystals: comparison of the size reduction effectiveness of a novel combinative method with conventional top-down approaches. Eur J Pharm Biopharm. 2012: 81(1): 82-90.

Savjani KT, Gajjar AK and Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharmaceutics. 2012.

Suman K, Chandrasekhar P and Balaji S. Drug nanocrystals: a novel formulation approach for poorly soluble drugs. International Journal of Pharm Tech Research 2009: 1(3): 682-694.

Vuppalapati L, Cherukuri S, Neeli V, Reddy YP and Reddy KB. Application of central composite design in optimization of valsartan nanosuspension to enhance its solubility and stability. Current drug delivery. 2016: 13(1): 143-157.

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