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Original Article

FORMULATION AND EVALUATION OF STABILIZED EPROSARTAN NANOSUSPENSION

M. SANTHOSH RAJA[1*], K. VENKATARAMANA[2]

[1]University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur 522510, India, [2]A. S. N. Pharmacy College, Burripalem Road, Tenali, Guntur 522201, India
Email: santhosh.raja88@gmail.com

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ABSTRACT

Objective: The objective of the current study is to enhance the solubility of Eprosartan mesylate a BCS Class II drug by employing the nanoprecipitation technique.

Methods: Polymeric nanoparticles of Eprosartan mesylate were prepared by precipitation technique with various polymers like PVP K30, HPMC K15M, and Eudragit L100 in various ratios. The incompatibility issues which may arise between the drug and polymers were tested by differential scanning calorimetry (DSC). The formed nanosuspensions were evaluated for various parameters like particle size, zeta potential, drug content, and dissolution testing.

Results: Among all the nanosuspension formulations, E12 formulation prepared with Eudragit L 100 showed better evaluation characteristics. SEM and DSC analysis showed no major interactions with the excipients. The maximum drug release was showed at 12h. The formulation E12 showed the particle size of 81.5±5.5 nm and zeta potential of-55.1mv.

Conclusion: The nano-precipitation method improved the dissolution as well as the bioavailability of Eprosartan mesylate nanosuspension.

Keywords: Bioavailability, Dissolution, Nanoprecipitation, Eprosartan mesylate, Eudragit

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INTRODUCTION

Administration of medicine through oral route is the most preferred method as it is best, convenient owing to its ease of administration, less pronounced adverse effects, easy intake, and patient compliable. In recent years significant effort has been focused on the improvement of new drug delivery systems [1]. Among the newer drug substances, nearly 40% of them are hydrophobic. The preparation and formulation of nanosuspension, which shows a substantial increment in solubility and permeability, is the best approach to increase bioavailability. Pharmaceutical nano-suspension is defined as submicron colloidal dispersions of nano-sized drug particles stabilized by surfactants, which consist of the hydrophobic drug without any matrix material [2-7]. In the nanoprecipitation method, simply a drug is dissolved in a suitable solvent and then the drug solution is mixed with anti-solvent (in which drug is insoluble) in the presence of surfactant. Rapid addition of drug solution to such anti-solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous nano-sized or crystalline drug [8]. Nanoprecipitation method gives many advantages like a simple process, low energy consumption, low cost of equipment, ease of scale-up, and offers stable products. Eprosartan mesylate is a BCS class II drug which has low solubility but high permeability [9-11]. Various studies on Eprosartan have shown an improvement in solubility and dissolution by the preparation of nanosuspensions [12, 13], SMEDDS [14, 15], and solid dispersions [16]. To avoid the toxicity of organic solvents, PEG is preferred as a diffusive phase. The aim of the present study is to formulate and evaluate nanosuspension of Eprosartan mesylate by nanoprecipitation method using PVP K30, HPMC K15 M, and Eudragit L 100.

MATERIALS AND METHODS

Materials

Eprosartan mesylate is obtained as a gift sample from J. B. Chemical and Pharmaceuticals Ltd, Mumbai, PVP K30, HPMC K15 M were procured from Loba chem. Pvt Ltd, Mumbai, Eudragit L 100 is a gift sample from Evonik Industries, Mumbai, Poloxamer 188 is procured from BASF, Mumbai, and all other ingredients used in the preparation were of analytical grade.

Methods

Formulation of eprosartan mesylate nanosuspension

Polymeric nanoparticles have been prepared by employing the nanoprecipitation technique [10]. A predetermined quantity of polymers as mentioned in table 1 are dissolved in 15 ml of PEG 200 with the help of a vortex mixer for 5 min duration to form into a diffusion phase. To the above-formed diffusion phase, accurately weighed 200 mg of the drug is added and see that the drug was completely dissolved in it. The aqueous phase is prepared by dissolving Poloxomer 188 (0.5% solution) in water, which is a non-solvent. The diffusive (PEG) phase is slowly transferred into the aqueous phase (35 ml) under stirring at 1000 RPM. After continuous stirring for abour30 min of stirring the mixture is homogenized under a high-speed homogenizer for 30 min at 7000 RPM. The resultant suspension is preserved and used as such for further study.

Evaluation of eprosartan nanosuspension

Particle size analysis

Total formulations of the drug were exposed to Scanning Electron Microscopy (SEM) for particle size determination and particle size had been determined and recorded [17].

Zeta potential

Zeta potential is a measure of the charge on the electrical double layer of the nanoparticle, which indicates the various stability concerns. Zeta potential measurements have been conducted at a temperature of 25 °C along with an electric field strength of 23 V/m, using Zetasizer (Malvern).

Percentage Entrapment efficiency

The % entrapment is determined by taking around 2 ml formulation into Nessler's cylinder tube (10 ml) and centrifuged at 2000-3000 RPM for 4 h. The supernatant layer formed after centrifugation is filtered using Whatman filter paper (No: 41) and diluted using Phosphate buffer (6.8 pH) up to 10 ml and the resultant solution for drug content was analyzed at specific lambda max of the drug utilizing UV visible spectrophotometer (Systronics 2202) for already

developed method. These tests were replicated 3 times and the result was recorded. % EE was calculated using the below formula

$$\% \text{ EE} = \frac{\text{Total drug content} - \text{Free drug}}{\text{Total drug used}} \text{ X } 100$$

Table 1: Formulation of eprosartan mesylate nanosuspension

Formulation code	Eprosartan mesylate (mg)	Polymer (%)			Stabilizer (%) poloxamer 188
		PVP K 30	HPMC K 15 M	EUDRAGIT L 100	
E1	200	0.5	--	--	0.5
E2	200	1.0	--	--	0.5
E3	200	1.5	--	--	0.5
E4	200	2.0	--	--	0.5
E5	200	--	0.5	--	0.5
E6	200	--	1.0	--	0.5
E7	200	--	1.5	--	0.5
E8	200	--	2.0	--	0.5
E9	200	--	--	0.5	0.5
E10	200	--	--	1.0	0.5
E11	200	--	--	1.5	0.5
E12	200	--	--	2.0	0.5

***In vitro* dissolution studies**

Drug release from the nanosuspension formulations was studied using an 8 station dissolution test apparatus (Electro lab TDT 08L) employing a USP II type paddle stirrer at a speed of 50 rpm and 37±1 °c. The dissolution medium consisted of a phosphate buffer of pH 6.8 (900 ml). The drug release from various nanosuspension formulations at pre-specified time intervals was measured from the developed and validated method by UV visible spectrophotometer (Systronics 2202). The dissolution experiments were conducted in triplicate. The dissolution data were fitted into various release kinetics like zero order, first order, Higuchi, and Peppas models to describe various release patterns [18, 19].

Attenuated total reflectance studies

The pure Eprosartan mesylate powder was taken and the ATR spectrum was recorded in Bruker instrument, which was compared to that of reference, and the ATR spectrum of final formulation was recorded priory to identify the compatibility issues between the API and selected excipients.

Differential scanning calorimetry

DSC scan of the pure drug was conducted using an automatic thermal analyzer system, accurately weighed about 5 mg of Eprosartan Mesylate was transferred and the scans were recorded. The entire samples were run at a scanning rate of 10˚C/min from 25-250˚C. The DSC was conducted for final formulation also to identify the compatibility issues [20].

RESULTS AND DISCUSSION

Particle size

All the formulations prepared were in the nanoparticles range and the best formulation i.e. E12 showed particle size of 81-95 nm were shown in table 2 and fig. 1, the satisfactory zeta potential of 55.1±1 mv (fig. 2) and percentage drug entrapped was 94.51.

Table 2: Evaluation parameters for eprosartan nanosuspension

Formulation	Particle size (nm)	Zeta Potential (mv)#	% Drug entrapped
E1	321-347	10.4±1	88.51
E2	331-321	12.2±2	85.41
E3	391-314	12.2±2	86.42
E4	265-284	10.5±3	87.28
E5	158-178	41.2±1	81.24
E6	167-148	41.2±3	83.66
E7	191-205	43.2±2	81.24
E8	101-124	41.2±2	82.57
E9	100-128	45.2±1	92.64
E10	121-134	42.2±1	90.24
E11	98-104	52.4±3	93.47
E12	81-95	55.1±1	94.51

mean±SD, n=3

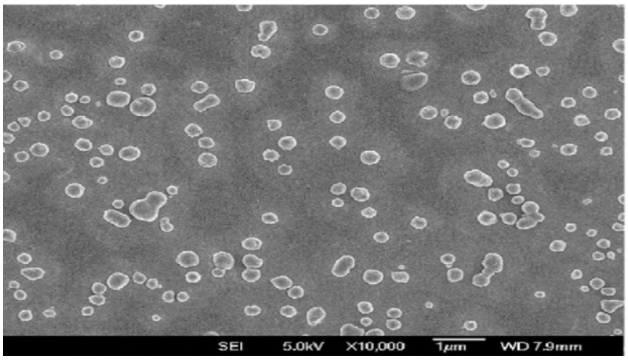

Fig. 1: SEM image of eprosartan mesylate nanosuspension (E12)

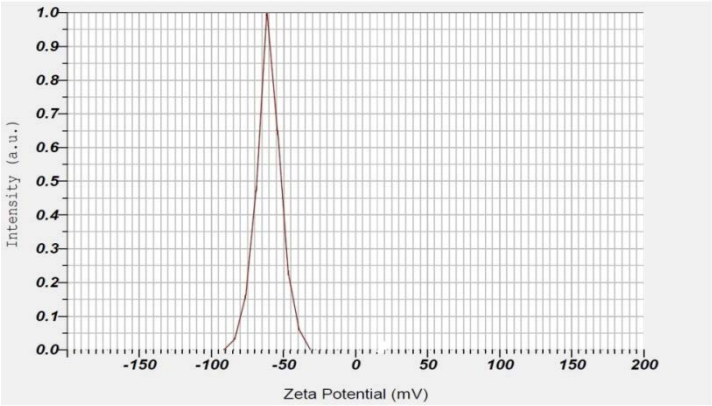

Fig. 2: Zeta potential graph of eprosartan mesylate nanosuspension (E12)

***In vitro* dissolution studies**

The drug release from various formulations was shown in fig. 3, 4, 5 and the drug release characteristics are shown in table 3. The drug release profiles showed different values; the formulations prepared with varied concentrations Eudragit L 100 i.e. E9, E10, E11 and E12 showed percent drug release of 100.01±2.04, 99.21±2.73, 98.41±2.04, 99.53±1.98 at the end of 7th, 8th, 10th and 12th hour respectively. Based on the above release pattern the E12 the formulation prepared with 2 % of Eudragit L 100 showed a release pattern according to the prescribed limits.

The entire dissolution data is fitted into various kinetic models to describe the release mechanisms. The zero-order kinetic model shows the correlation coefficient r^2 values in the range of 0.9336 to 0.9856, indicating the drug release mechanism followed zero-order kinetics. The first order r^2 lies in the range of 0.7703 to 0.9405 indicating that the drug release followed zero-order kinetics. The r^2 values of the Higuchi model range from 0.9494 to 0.9941, indicating the drug release mechanism is diffusion. The n value of Peppas kinetics showed the majority lies in the range of 0.5–1 indicating nonfickian form of diffusion. Based on the above all parameters the E12 was selected as the best formulation and proceeded for further studies.

The Nanoprecipitation method was successfully employed and a stabilized nanosuspension was formed by using the polymers were reported in various studies [11].

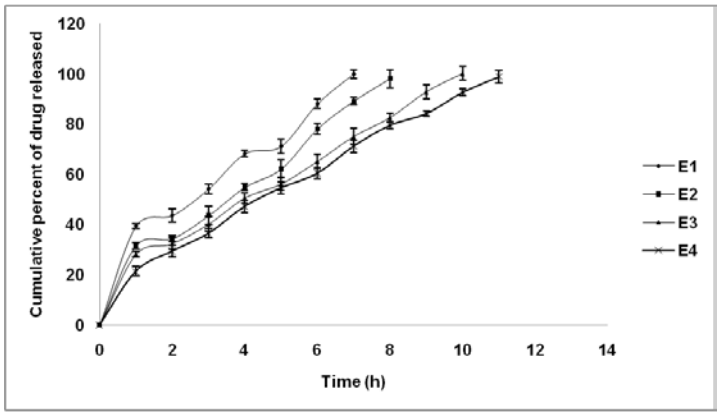

Fig. 3: Drug release plot of eprosartan mesylate from formulations prepared with PVP K30 (mean±SD; n=6)

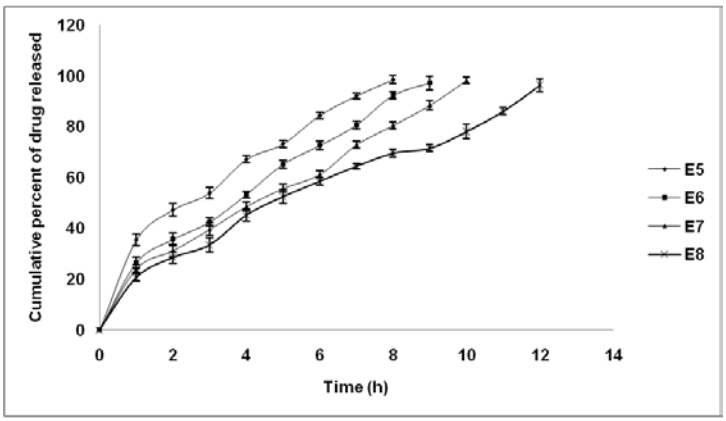

Fig. 4: Drug release plot of eprosartan mesylate from formulations prepared with HPMC K 15 M (mean±SD; n=6)

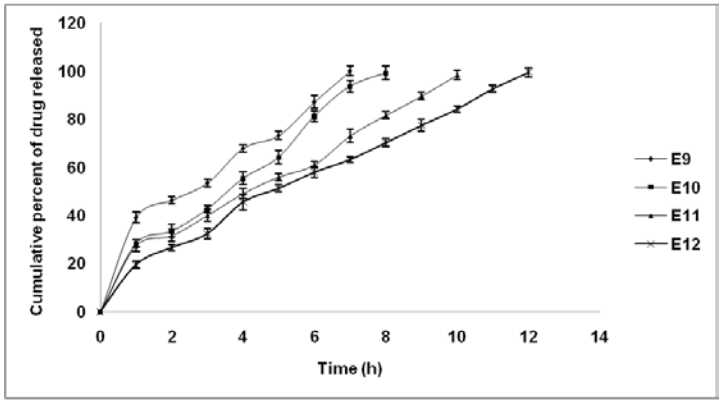

Fig. 5: Drug release plot of eprosartan mesylate from formulations prepared with Eudragit L 100 (mean±SD; n=6)

Table 3: Release characteristics of eprosartan nanosuspension formulations

Formulation code	Correlation coefficient values (R^2)				Diffusion exponent (n) value of peppas
	Zero-order	First-order	Higuchi's model	Peppas model	
E1	0.9363	0.9168	0.9707	0.9230	0.48
E2	0.9702	0.7850	0.9494	0.9200	0.58
E3	0.9766	0.8893	0.9639	0.9548	0.58
E4	0.9839	0.7824	0.9702	0.9883	0.66
E5	0.9336	0.8534	0.9941	0.9861	0.50
E6	0.9752	0.8672	0.9740	0.9804	0.61
E7	0.9810	0.7730	0.9657	0.9783	0.62
E8	0.9699	0.8241	0.9770	0.9880	0.62
E9	0.9353	0.9405	0.9765	0.9396	0.48
E10	0.9796	0.8488	0.9453	0.9443	0.64
E11	0.9758	0.7703	0.9628	0.9560	0.58
E12	0.9856	0.9093	0.9672	0.9872	0.67

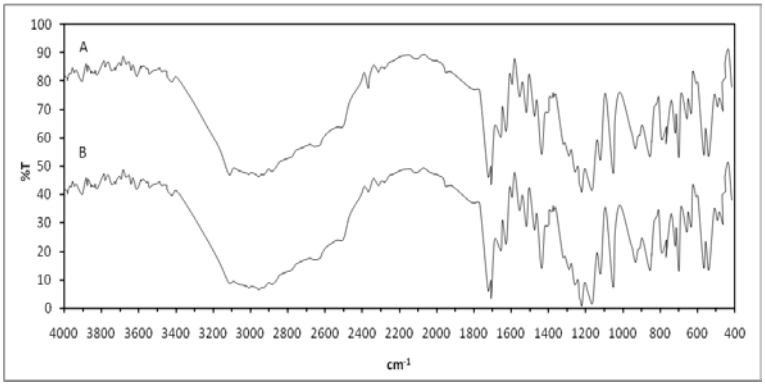

Fig. 6: ATR Spectrum of eprosartan and along with excipients, *A = Pure eprosartan, B = combination of eprosartan along with excipients

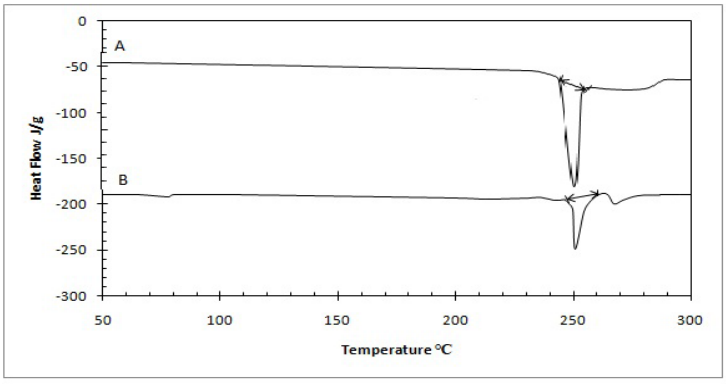

Fig. 7: DSC Thermogram of Eprosartan and along with excipients, *A = Pure Eprosartan, B = combination of Eprosartan along with excipients

Attenuated total reflectance studies

ATR spectrums of Pure Eprosartan mesylate and the final formulation are shown in fig. 6. From these graphs, it is clear that there are no interactions between the excipients and the drug, as there are no variations in the spectra.

Differential scanning calorimetry

DSC scans of pure drug Eprosartan as in fig. 7, indicated the melting point at 249.2 °C and the final formulation also shows the characteristic peak at 250.2 °C showing no major shift in peaks indicating the compatibility of the polymers.

CONCLUSION

Nanosuspension of Eprosartan mesylate was successfully prepared by using the precipitation method. Among all the formulations, E12 prepared with Eudragit RL100 at 2.0% concentration showed a better release pattern and satisfactory zeta potential and particle size. The prepared formulations showed satisfactory dissolution and other evaluation characteristics. Hence the Eprosartan mesylate nanosuspension can be conveniently administered as an oral drug delivery system.

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Nil

AUTHORS CONTRIBUTIONS

Mr. M. Santhosh Raja the guarantor of this study, has designed, carried out the experiment, analyzed the results, and contributed in the preparation and revision of the manuscript. Dr. K. Venkataramana has designed, supervised the experimental process, and reviewed the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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