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Research Article

DESIGN AND DEVELOPMENT OF NEBIVOLOL HCl NANOSUSPENSION

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ABSTRACT

The purpose of present research work was to formulate and evaluate nanosuspension of Nebivolol hydrochloride in order to enhance its solubility as well as bioavailability. Various nanosuspension batches were prepared by the nanoprecipitation technique. The prepared nanosuspension was evaluated parameters like particle size, polydispersity index, zeta potential, saturation solubility and entrapment efficiency. The Particle size and Zeta potential in optimized nanosuspension were found to be 207.2 nm and 34.89 mV. From the study, suggested nanosuspension is an alternative approach to improve the solubility and bioavailability of Nebivolol HCl.

Key-words: Nebivolol HCl, Nanoprecipitation, and Nanosuspension.

INTRODUCTION

Most of the antihypertensive drug candidates are insoluble in nature and possessing low solubility and bioavailability due to high first-pass hepatic metabolism. Nebivolol hydrochloride is third generation beta-blocker, with selective beta-1 adrenoreceptor antagonist and high potential to release nitric oxide from cardiovascular endothelium. Nebivolol hydrochloride is practically insoluble in water. The plasma half-life is about 8-10 hr[1,2]. A nanosuspension contains submicron colloidal nanosized drug particles, which are stabilized by surfactants. They are applied in oral and topical use or parenteral and pulmonary administration. In the present research investigation, nanosuspensions were prepared by nanoprecipitation method. The prepared nanosuspension was characterized in terms of particle size, polydispersibility index, zeta potential, % entrapment efficiency and saturation solubility. SC7620, Unitec, 10 4min, gold coating. Therefore, the primary aim of this work was to develop and evaluate nanosuspension of Nebivolol HCl [3].

MATERIALS AND METHODS

Nebivolol hydrochloride was received from Cadila Ltd (Ahmedabad, India). Tween 80, and Hydroxy propylmethylcellulose (HPMC E3) were obtained from S.D. Fine Chemicals Limited (Mumbai, India). Analytical grades of acetone, dichloromethane, ethyl acetate, and isopropyl alcohol were procured from S. D. Fine Chemicals Limited (Mumbai, India). For Experimental study, Double Distilled water is used.

Preparation of Nebivolol HCl loaded nanosuspension

Nebivolol HCl loaded nanosuspension was prepared by nanoprecipitation technique. Nebivolol HCl was dispersed in a good solvent and sonicated for few seconds. This organic solution was filtered through Whatman filter paper (0.22 µm). The prepared Nebivolol HCl solution was injected by the syringe into a bad solvent containing each specific concentration of polymer and/ or surfactant with continuous magnetic stirring. The precipitation starts at once upon mixing and forming the nanosuspension with slight bluish appearance [4-7].

Characterizations of Nebivolol HCl loaded nanosuspension

Particle Size, Size Distribution and Zeta Potential measurement

For all batches of Nebivolol HCl loaded nanosuspension particle size, its distribution and zeta potential were determined using Zetatrac (Microtac Inc., USA). 100 gm of sample was diluted to 10 mL with double distilled water. All the samples were subjected to a short period of sonication to lessen any aggregation if present, using a bath sonicator. The study was repeated in triplicates and average values were summarized [4,5,6,8].

Determination of saturation solubility

The excess amount of various formulation batches of Nebivolol HCl loaded nanosuspension was added to 10 mL of phosphate buffer pH 6.8. Samples were sonicated for 5 sec and stirred in a isothermal shaker bath (37±0.3 °C) for 48 h. Samples were then centrifuged at 4500 rpm for 15 min and filtered it, diluted suitable amount using phosphate buffer pH 6.8 solution and analyzed using double beam–UV spectrophotometer against phosphate buffer pH 6.8 as blank. The study was repeated in triplicates and average values were summarized [4].

Drug entrapment efficiency (%) study

Aliquots of (2 mL) freshly prepared Nebivolol HCl loaded nanoususpension was centrifuged at 2500 rpm for 25 min and the supernatant was removed. The solution was filtered and diluted it appropriately with phosphate buffer pH 6.8 and the amount of unincorporated drug was determined using double beam UV-spectrophotometer against phosphate buffer pH 6.8 as blank or control of nanosuspension. The study was repeated in triplicates and average values were summarized [7,8].

Entrapment efficiency (EE %) was calculated from the following equation:

$$\% \text{ Entrapment efficiency} = \frac{\text{Weight of Initial drug} - \text{Weight of Free drug}}{\text{Weight of Initial drug}} \times 100$$

Scanning Electron Microscope study

The shape and surface morphology of Nebivolol HCl loaded nanosuspension was determined by Scanning Electron Microscopy (SEM) study. SEM stub was prepared using double-sided adhesive tape and coated with gold at 10 mA for 4 min through a sputter-coater (Model No. SC7620). The samples are examined at 15.00 kV accelerating voltage at different magnifications [9--11].

RESULTS AND DISCUSSION

Preliminary study

Influence of the stabilizer on nanosuspension

Screening for an optimal stabilizer is very important for the product quality. The stabilizer was mixed with nanosuspension system because it inhibited particulate aggregation as well as Ostwald ripening. So in the present study, different types of stabilizers were employed at a constant amount of stabilizers. As shown in a Figure 1, Tween 80 showed the highest particle size reduction; subsequently, followed by Poloxamer 407. Poloxamer 407 enhanced the wettability of Nebivolol HCl and coated newly formed nanoparticulate surfaces very efficiently; hence, it was resolute to employ both Tween 80 and Poloxamer 407 to develop Nebivolol HCl loaded nanosuspension [4].

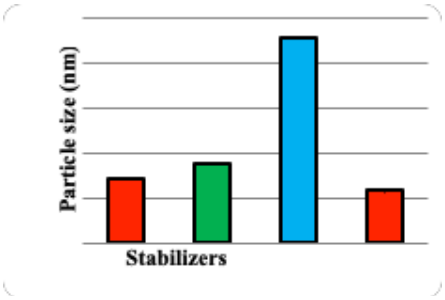

Figure 1: Results of particle size using different stabilizers

The solubility of the drug was carried out in various organic solvents (Acetone, Ethanol, and Methanol) to explore the most appropriated solvent, which had a maximum drug loading ability and provides greater supersaturation that would provide in rapid nucleation and precipitation. It was seen that amongst the various organic solvent utilized, Acetone exhibited the highest solubility for Nebivolol HCl and was chosen as the organic solvent phase. Because of poor solubility of Nebivolol HCl in water (bad solvent) and high solubility of water with acetone (good solvent) water was then chosen as the antisolvent phase to begin the precipitation process [4].

Table 1: Results of Nebivolol HCl nanosuspension

Code	Solvents	S-AS Ratio	Particle size (nm)	Polydispersibility Index	Zeta potential (mV)	%Saturation solubility	% Entrapment efficiency
B01	Acetone	1:10	325.6±1.02	0.139±0.03	28.34±0.102	90±0.003	88.8±1.201
B02	Acetone	1:20	291.7±3.66	0.245±1.035	32.46±1.36	78±0.145	62.06±0.391
B03	**Acetone**	**1:30**	**207.2**±0.22	**0.150**±0.97	**34.89**±0.01	**91±0.014**	**96.38±0.007**
B04	Acetone	1:40	250.39±4.9	0.185±0.03	37.14±6.092	55±0.69	49.44±0.087
B05	Acetone	1:50	297.8±7.02	0.105±5.06	36.27±2.08	80±1.20	48.42±0.102
B06	Methanol	1:10	319.54±0.9	0.111±7.55	41.92±0.041	55±0.008	58.24±0.304
B07	Ethanol	1:10	347.18±1.3	0.367±0.39	45.79±1.07	69±0.096	70.95±0.708
B08	Ethanol	1:20	393.2±2.07	0.709±0.01	30.31±2.084	66±0.105	81.12±0.149
B09	Ethanol	1:30	409.7±0.89	0.221±0.205	33.64±4.214	57±0.032	64.6±0.687
B10	Ethanol	1:40	468.3±0.64	0.367±0.274	26.78±1.35	59±0.253	54.43±0.452
B11	Ethanol	1:50	496.9±1.04	0.195±4.08	29.88±2.68	54±0.314	49.35±0.678

The results are mean±SD, (n=3)

Effect of the types of solvent and antisolvent

Total 11 Nebivolol HCl nanosuspension batches of various organic solvents with antisolvent water at varying ratios were prepared and results are obtained as per shown in Table 1. The formulation batch B03 exhibited 91%Saturation solubility and 96.38%Entrapment efficiency that was greater as compared to other organic solvents with the different S-AS ratio. Acetone is highly miscible with water and readily helps in the precipitation process. In this study, Acetone and Water were chosen as the optimized organic solvent and antisolvent phase at 1:30 ratio. When S/AS as volume ratio was increased from 1:10 to 1:30, the decrease in particle size was observed due to new nuclei was formed and growth of nuclei happen simultaneously. For the consequent growth, a high solvent to antisolvent ratio would enhance the diffusion distance for growth species, thus, diffusion becomes the limiting step for nuclei growth [4].

The morphological characterizations of prepared optimized nanosuspension showed the small spherical shape and uniform size distribution as observed in the SEM photograph.

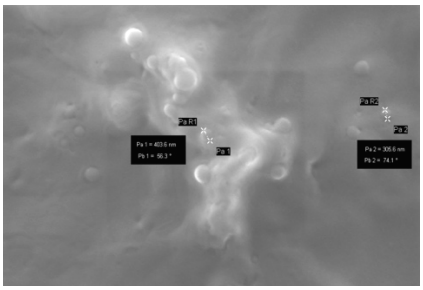

Figure 2: SEM Image of Nebivolol HCl nanosuspension

An optimized batch contained 15 mg Poloxamer 407 and 10 mg of Tween 80. The particle size distribution of the optimized batch was found to be uniform because of the Polydispersity index narrowed down to 0.15. The optimized batch had particle size 207.2 nm. The zeta potential of the nanoparticles was found to be 34.89 mv. High zeta potential values should be achieved to ensure a high-energy barrier and favour a good stability ultimately no aggregation took place of nanosize particles in formulation [4].

Figure 3: Optimized Nebivolol HCl nanosuspension

Table 2: Results of optimized batch Nebivolol HCl nanosuspension

%Saturation solubility	%Entrapment efficiency	Particle size (nm)	Zeta potential (mV)	Polydispersity index
91%	96.38%	207.2	34.89	0.15

CONCLUSION

Different Nebivolol HCl loaded nanosuspensions were prepared using the nanoprecipitation technique. The formulation B03 showed the maximum drug entrapment efficiency with a mean particle size and zeta potential of 207.2 nm and 34.89 mv, respectively. The results of SEM study and zetasizer confirmed that particles are the nanosize range. The above investigation leaves a future extension for refining innovation that can additionally be utilized for the arrangement of different other nano dosage form in pharmaceutical products.

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